EXHIBIT 2

REVIEW ARTICLE

Deborah J. Culley, M.D., Editor

ANESTHESIOLOGY

Clinical Effectiveness of Liposomal Bupivacaine Administered by Infiltration or Peripheral Nerve Block to Treat Postoperative Pain

A Narrative Review

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ABSTRACT

The authors provide a comprehensive summary of all randomized, controlled trials (n = 76) involving the clinical administration of liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, USA) to control postoperative pain that are currently published. When infiltrated surgically and compared with unencapsulated bupivacaine or ropivacaine, only 11% of trials (4 of 36) reported a clinically relevant and statistically significant improvement in the primary outcome favoring liposomal bupivacaine. Ninety-two percent of trials (11 of 12) suggested a peripheral nerve block with unencapsulated bupivacaine provides superior analgesia to infiltrated liposomal bupivacaine. Results were mixed for the 16 trials comparing liposomal and unencapsulated bupivacaine, both within peripheral nerve blocks. Overall, of the trials deemed at high risk for bias, 84% (16 of 19) reported statistically significant differences for their primary outcome measure(s) compared with only 14% (4 of 28) of those with a low risk of bias. The preponderance of evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics.

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The pain of many surgical procedures extends beyond the duration of analgesia provided with a single administration of standard local anesthetic. Bupivacaine hydrochloride is currently the longest-acting local anesthetic approved by the U.S. Food and Drug Administration (Silver Spring, Maryland), with a duration of up to 18 h when administered in some peripheral nerve blocks. While multiple adjuvants such as dexamethasone and dexmedetomidine have been proposed, there is currently no Food and Drug Administration–approved medication that reliably extends the duration of action of local anesthetic beyond 24 h.[1] However, by encasing standard local anesthetic within various carriers, a sustained release may be achieved that extends the analgesic duration, perhaps to multiple days. Many such formulations have been described,[2] but only a single sustained released local anesthetic is currently approved for clinical use by the Food and Drug Administration: liposomal bupivacaine. Currently, a number of publications are available that review the use of liposomal bupivacaine, but all involve a specific topic area (*e.g.*, shoulder surgery), and therefore include only a small subset (n = 7 to 27 studies) of available randomized, controlled trials.[3–7] The current article aims to provide a comprehensive summary of all the published randomized, controlled trials (n = 76) involving the clinical use of liposomal bupivacaine when administered to control acute postsurgical pain.

Liposomal Local Anesthetic

Liposomes consist of a hydrophilic head and two hydrophobic tails and come in multiple permutations. Unilamellar vesicles are created with a single outer bilayer—effectively a hollow sphere—that may hold medication within its cavity.[8] Far larger multilamellar liposomes are basically a sphere containing additional nested concentric spheres, much like a Russian matryoshka or babushka doll.[9] In contrast, nonconcentric multivesicular liposomes are essentially an uncoordinated mass creating a myriad of cavities that may be filled with medication.[10] Their large size creates a "medication depot," which gradually discharges the contents with natural liposome membrane breakdown. This creates a sustained release, which enables prolonged pharmacologic effects. First proposed as a medication carrier in 1965, multivesicular liposomes have been used to encapsulate pharmaceuticals as diverse as ibuprofen, neostigmine, chemotherapeutics, and opioids.[11] In 2004, liposome morphine (DepoDur; Pacira Pharmaceuticals, USA) became the first liposome-encased medication to be approved for postoperative analgesia by the U.S. Food and Drug Administration.[12–14]

Extending the duration of local anesthetic (lidocaine) using liposomes was first proposed in 1979,[15] followed a year later by the first *in vivo* use in guinea pigs (dibucaine),[16] and the first use in humans in 1988 (topical tetracaine).[17] The first report of treating postoperative pain with liposomal local anesthetic occurred in 1994: subjects undergoing major abdominal, thoracic, or orthopedic surgery were given a single epidural injection of either liposomal bupivacaine 0.5% or "standard" bupivacaine hydrochloride

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0.5% (subject- and observer-masked, although not randomized).[18] Subjects receiving unencapsulated bupivacaine experienced a mean ± SD duration of analgesia of 3.2 ± 0.4 h *versus* 6.3 ± 1.1 h for those receiving liposomal bupivacaine ($P < 0.05$). Such encouraging results helped propel future preclinical and human subject research.[19]

Clinical Availability

In 2011 the U.S. Food and Drug Administration approved a liposome encapsulated bupivacaine (Exparel; Pacira Pharmaceuticals) with an explicit indication: single-dose infiltration into the surgical site to produce postsurgical analgesia in adults.[20] The label was subsequently expanded to explicitly approve use in transversus abdominis plane blocks, as well as interscalene blocks specifically for shoulder surgery.[21] The medication is provided in 20-ml ampules that contain the maximum-approved dose: 266 mg (13.3 mg/ml or 1.33%).[22] Of note, the milligram dose is expressed as the free base, so 266 mg of liposomal bupivacaine is roughly equivalent to 300 mg of unencapsulated bupivacaine hydrochloride.[23] Each ampule should be administered within 4 h of opening, diluted with normal saline or lactated Ringer's solution (up to 1:14), and administered with a 25-gauge or larger bore needle.[24] Local anesthetics other than bupivacaine hydrochloride may result in a premature release of bupivacaine from the liposome vesicles if administered together locally.[24] Therefore, liposomal bupivacaine should be administered after a minimum delay of 20 min after injection of a different local anesthetic.[25] In contrast, bupivacaine hydrochloride may be administered simultaneously—even admixed within the same syringe—up to a maximum dose of 50% of the liposomal bupivacaine.[26]

Liposomal bupivacaine exhibits a biphasic plasma peak when infiltrated directly into tissues.[27] The initial peak occurring within 1 to 2 h is due to the extra-liposomal bupivacaine hydrochloride included in every ampule (less than 3% of all bupivacaine in vial), which also provides an onset similar to unencapsulated bupivacaine.[28] This is followed by a second peak due to the slow release of bupivacaine hydrochloride from the liposomes at nearly twice the plasma concentration 24 to 48 h after administration compared to unencapsulated bupivacaine (even longer with a mixture of encapsulated and unencapsulated bupivacaine).[26,27] Bupivacaine can still be detected within the plasma 3 to 14 days after administration, depending on the route, dose, and additional factors.[27,29,30] However, local pharmacologic effect does not necessarily mirror plasma concentration, and analgesic duration cannot be inferred from the time of bupivacaine detectability within the blood. For example, tissue infiltration with 150 mg of bupivacaine hydrochloride results in detectable plasma concentrations for over 72 h,[31] yet no clinical trial has demonstrated an analgesic effect of even 24 h duration: blood concentration is correlated with systemic toxicity, not local effect.[24] After liposome release, the bupivacaine absorption, distribution, metabolism, and excretion are similar to the bupivacaine hydrochloride formulation.[24]

Safety Profile

Due to the gradual—*versus* immediate—release of bupivacaine, determining the safety profile of liposomal bupivacaine requires medication-specific investigations.[32] Preclinical studies demonstrate a similar or larger margin of safety with liposomal bupivacaine than unencapsulated bupivacaine.[32–39] For example, in rabbits, roughly twice as much liposomal bupivacaine must be intravenously infused to induce seizures, ventricular tachycardia, and asystole compared with bupivacaine hydrochloride.[40] In humans, 823 subjects exposed to liposomal bupivacaine within 10 randomized, controlled trials involving surgical site infiltration experienced no more adverse events than subjects receiving bupivacaine hydrochloride,[41] a finding reproduced when liposomal bupivacaine was administered as part of a peripheral nerve block in 335 patients among six studies.[42] Liposomal bupivacaine appears to have no negative influence on wound healing when infiltrated into the surgical site,[43] and it is compatible with common implanted materials such as titanium, silicone, and polypropylene.[44,45]

While local anesthetic systemic toxicity can occur with liposomal bupivacaine,[46] it appears to have a favorable cardiac safety profile compared to bupivacaine hydrochloride.[47–51] In humans, there have been three suspected intravenous injections of liposomal bupivacaine, involving 150 to 450 mg of injectate intended for surgical site tissue infiltration after knee arthroplasty.[47] Other subjects within this study had mean bupivacaine plasma concentrations of 255 ng/ml (for 150 mg group) and 520 ng/ml (450 mg group). In contrast, the three subjects with suspected intravascular injections had concentrations of approximately 8,000 to 34,000 ng/ml. Yet none had symptoms or signs of local anesthetic toxicity, including no electrocardiogram/QTcF changes from baseline.[47] Toxicity has resulted from far lower doses of unencapsulated long-acting local anesthetics.[52–54]

Clinical Effectiveness

Early in the development of new medications and devices, case reports and retrospective studies are of great service to generate hypotheses that may then be tested with randomized, controlled trials. This was the case for liposomal bupivacaine during much of the last decade, with 28 of 30 (93%) of reviewed retrospective studies reporting positive findings.[55–84] However, in the last few years, there has been a substantial increase in the number of randomized, controlled trials, with 76 published at the time of this writing (tables 1–10). Given the new plethora of data from investigations with a design considered the accepted standard when evaluating medical interventions, this review will focus on published randomized, controlled trials.

Unfortunately, 30 (40%) of these trials were either unregistered or registered after enrollment, and 26 (35%) failed to define a primary outcome measure or had a significant problem with the definition (*e.g.*, discrepancy between registry and published article). Interpretation of results can be problematic for investigations lacking prospective registration and/or a predetermined primary outcome measure. The latter is critical in evaluating randomized, controlled trials with multiple endpoints (outcomes) since the risk of erroneously finding a difference when none truly exists (type I error) is greatly multiplied with each comparison without statistical control (*e.g.*, a Bonferroni correction).[85] To illustrate, one trial designated three daily variables during a 7 to 14 day period as coprimary outcomes without a statistical plan managing multiple endpoints, and reported *P* values greater than 0.05 for all but a single comparison (pain on postoperative day 2).[86] With 35 comparisons, the risk of erroneously finding at least one positive outcome is 83%; yet, within the abstract the single statistically significant finding was emphasized, greatly skewing interpretation of the results. Designating *a priori* and subsequently focusing on a single comparison—the primary outcome—reduces the risk of a type I error to (typically) 5% (minimizing the type II risk as well).

Infiltration with Liposomal Bupivacaine *versus* Placebo

There are 12 placebo-controlled randomized trials investigating the use of liposomal bupivacaine infiltrated into the surgical site to control postoperative pain after procedures of the trunk, extremities, and dentition (tables 1 and 2).[86–97] Seven of the 12 (58%) failed to find a statistically significant difference for the primary outcome measure between active and placebo treatments,[86–92] and all but one had an overall low risk of bias based on the Cochrane risk-of-bias tool for randomized trials.[98,99] In contrast, 5 of the 12 (42%) reported a statistically significant difference between active and placebo treatments for either the primary outcome measure or most of the outcomes (for studies which did not predefine a specific primary outcome); and, all five of these randomized, controlled trials had a high risk of bias based on the Cochrane tool.[93–97] We will discuss the study methodology and interpretation of results for key investigations and then draw conclusions regarding clinical effectiveness.

The Food and Drug Administration used data from three pivotal phase III studies to evaluate—and ultimately approve—the use of liposomal bupivacaine for surgical site infiltration.[94,95] Two of these randomized, controlled trials were published in the peer-reviewed literature and reported that liposomal bupivacaine infiltration compared with placebo resulted in reduced pain scores for up to 36 and 72 h after bunion removal and hemorrhoidectomy, respectively (table 1).[94,95] Total opioid use, time until first opioid use, and patient satisfaction were all improved with liposomal bupivacaine. However, two notable factors greatly influence interpretation of these results. The first is that the pain and opioid consumption outcomes were calculated using the area under the receiver operating characteristics curve (AUC), which essentially compares the integral of all values over a period of time between the two treatments. If differences are large for a short period of time but nonexistent subsequently, the AUC can still be statistically significant over the total study period, giving the impression of extended duration when none exists. Indeed, the Food and Drug Administration clinical review stated that for the hemorrhoidectomy study, "although the primary endpoint was the AUC for pain intensity during the first 72 h postoperatively, the two treatments (bupivacaine liposomal and placebo) differed significantly and clinically only during the first 24 h" (fig. 1A).[100] Similarly, for this same study, cumulative opioid use was reported as lower at 0 to 72 h, yet there is only an improvement within the first 12 postoperative hours, and there are virtually no differences between the groups over the subsequent 60 h (group differences of 0.2 to 1.2 mg during each 12-h period, with the treatment group requiring more opioid in three of the five 12-h periods).[95] The same issue may be found with the pivotal bunion removal randomized, controlled trial, with no differences in effect on pain measures after 24 h (fig. 1B).[94,100] So, while it is reassuring that liposomal bupivacaine was an improvement over placebo for up to 24 h, it is not compelling evidence for clinical use.

A second important and frequently overlooked factor when interpreting the results of these two placebo-controlled trials is that pain score AUCs were not determined exclusively using actual pain scores, but rather with the "windowed worst-observation-carried-forward + last-observation-carried-forward ("wWOCF+LOCF") imputation method" in which "NRS [Numeric Rating Scale] scores were recorded within a time window for patients who took postsurgical rescue pain medication (6 h, based on the half-life of rescue medication…) and replaced by the 'worst' observation (*i.e.*, the highest pain score before taking their first rescue medication)." Furthermore, missing scores were replaced by one of three methods including last-observation-carried-forward. While imputation techniques such as last-observation-carried-forward were accepted by the Food and Drug Administration at the time of the original liposomal bupivacaine submission, it subsequently determined that "single imputation methods like last observation carried forward…should not be used as the primary approach to the treatment of missing data" because it can result in an "exaggerated positive effect, biased in favor of treatment."[101]

Moreover, the windowed worst-observation-carried-forward imputation—while unquestionably a valid statistical technique—remains an artificial construct of the randomized, controlled trial and decreases generalizability of the results to patients outside of the investigation. For

Table 1. Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Placebo

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Lumbar spine (n = 50)	Liposomal bupivacaine 266 mg in 60 ml	Saline 60 ml	Morphine mg equivalent 0–72 h	12 mg	13 mg	0.40	+	+	+	+	+	+	Study funding	Not registered	Brown[87]
Vaginal wall (n = 100)	Liposomal bupivacaine 266 mg (presumed) in 20 ml	Saline 20 ml	Defense and Veterans Pain Rating Score POD 1	1.0	1.0	0.59	+	+	+	+	+	+	None	Liposomal bupivacaine injection of 20 ml; but dose not specified	Jones[88]
			Defense and Veterans Pain Rating Score POD 3	2.0	1.0	0.20									
Molar extraction (n = 150)	Liposomal bupivacaine 133 mg in 10 ml	Saline 10 ml	Numeric Rating Scale AUC 0–48 h	172	195	0.23	+	+	+	+	+	+	Study funding; first author paid consultant; author company employee	Large number of protocol violations; data presented for intention-to-treat; per protocol results favored liposomal bupivacaine group	Lieblich[89]
Shoulder arthroplasty (n = 78)	Liposomal bupivacaine 266 mg in 20 ml	No infiltration	Morphine mg equivalent 0–24 h	35 mg	19 mg	0.01	+	+	+	+	+	+	None	All subjects had preoperative interscalene nerve block with ropivacaine 0.5% (15 ml)	Namdari[90]
Tonsillectomy (n = 33)	Liposomal bupivacaine 106 mg in 8 ml	No infiltration	35 "primary endpoints" designated, but none statistically significant with the exception of a single pain score on day 1				?	+	+	+	?	?	None	Outcome assessors possibly unmasked; multiple "primary endpoints" designated but all negative but a single pain score on day 1	Olson[86]
Cesarean delivery (n = 79)	Liposomal bupivacaine 266 mg in 80 ml	Saline 80 ml	Numeric Rating Scale with movement 48 h	4.0	3.5	0.72	+	+	+	+	+	+	Study funding	None	Prabhu[91]
Robotic sacrocolpopexy (n = 64)	Liposomal bupivacaine 266 mg in 30 ml	Saline 30 ml	VAS 18 h	1.5	2.1	0.52	+	+	+	+	+	+	None	None	(*Continued*) Yeung[92]

Table 1. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	P	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Statistically Significant Difference for Primary Outcome Measure															
Ankle open reduction internal fixation (n = 76)	Liposomal bupivacaine 266 mg (presumed) in 40 ml	Saline 40 ml	Not designated				-	+	+	+	?	-	First author paid consultant	Not registered; inadequate statistical plan with no primary outcome designated; outcome assessors and investigators were not masked to treatment group assignment	Davidovitch[93]
Hallux valgus osteotomy (n = 185)	Liposomal bupivacaine 120 mg in 8 ml	Saline 8 ml	Numeric Rating Scale AUC 0–24 h	197	220	< 0.01	-	+	+	?	+	-	Study funding; author company employee	Not registered; pain outcomes calculated with windowed-worst observation carried forward; missing pain scores replaced by imputation; pain scores not provided for any time points	Golf[94]
Hemorrhoid-ectomy (n = 186)	Liposomal bupivacaine 266 mg* in 30 ml	Saline 30 ml	Numeric Rating Scale AUC 0–72 h	142	203	< 0.01	-	+	+	?	+	-	Study funding; two authors company employees	Pain outcomes calculated with windowed worst-observation-carried-forward; missing pain scores replaced by imputation; pain scores not provided for any time points	Gorfine[95]
Retropubic sling (n = 109)	Liposomal bupivacaine 266 mg in 30 ml	Saline 30 ml	VAS 4 h	0.35	1.3	0.14	-	+	+	+	+	-	None	Primary outcome time points differ between registry and published article (registry time point provided in this table); authors questioned the cost–benefit ratio given very minimal improvements	Mazloom-doost[96]
Laparotomy (n = 67)	Liposomal bupivacaine 266 mg in 200 ml†	No infiltration	Primary outcome designated as both opioid use and pain scores with no designated time point				-	+	+	+	+	-	No funding statement provided; no author conflict of interest information provided	Not registered	Yalmanchili[97]

An additional publication (unregistered) reports adverse events from what appears to be an overlapping patient population,[205] and one study purports to be "randomized" but was actually sequential.[206] Secondary outcomes are presented in table 2.

*Dose reported as 300 mg, but this is chemically equivalent to 266 mg free base, which is described by nearly all investigations.[23] †A third treatment group not involving infiltration excluded from this chart (*e.g.*, continuous peripheral nerve block).

AUC, area under the receiving operator characteristics curve; POD, postoperative day; VAS, visual analogue scale. Cochrane Risk of Bias 2 abbreviations: O, overall risk of bias; R, bias arising from the randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in selection of the reported result.

Table 2. Secondary Outcomes for Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Placebo

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Lumbar spine (n = 50)	Liposomal bupivacaine 266 mg in 60 ml	Saline 60 ml	VAS POD 1–3	5.0	4.8	0.80	IV rescue	1.3	1.2	0.83	Days	3.6	3.7	0.25	Brown[87]
Vaginal wall (n = 100)	Liposomal bupivacaine 266 mg in 20 ml (presumed)	Saline 20 ml	Defense and Veterans Pain Rating Score POD 7	3.0	1.5	0.06	POD 0–7	113	102	0.81	Not reported				Jones[88]
Molar extraction (n = 150)	Liposomal bupivacaine 133 mg in 10 ml	Saline 10 ml	Numeric Rating Scale AUC 0–96 h	274	311	> 0.05	0–48 h	2.9	3.2	0.74	Not applicable (ambulatory procedures)				Lieblich[89]
Shoulder arthroplasty (n = 78)	Liposomal bupivacaine 266 mg in 20 ml	No infiltration	VAS 8 h	3.2	3.0	> 0.05	Intraoperative	12	11	0.17	Days	1.5	1.5	0.56	Namdari[90]
			VAS 24 h	4.2	4.0										
			VAS 72 h	2.9	3.5										
Tonsillectomy (n = 33)	Liposomal bupivacaine 106 mg in 8 ml	No infiltration	VAS POD 1	3.1	4.9	0.04	Oxycodone POD 1	18	21	>0.05	Not applicable (ambulatory procedures)				Olson[86]
			VAS POD 2	4.2	5.1	0.29									
			VAS POD 3	5.1	5.4	0.63									
Cesarean delivery (n = 79)	Liposomal bupivacaine 266 mg in 80 ml	Saline 80 ml	Numeric Rating Scale at rest 28 h	5	4	0.50	0–48 h	38	38	0.44	Percent discharged by POD 3	18%	10%	Not reported	Prabhu[91]
			Numeric Rating Scale at rest 48 h	3	2.5	0.14									
Robotic sacrocolpopexy (n = 64)	Liposomal bupivacaine 266 mg in 30 ml	Saline 30 ml	VAS average POD 1	2.9	3.4	0.82	0–72 h	27	18	0.90	Not reported, but 5 and 4 subjects were discharged home with a Foley catheter after failing a voiding trial ($P > 0.99$)				Yeung[92]
			VAS average POD 2	2.3	2.5	0.80									

(*Continued*)

Table 2. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Pain Scores: Measure	Pain Scores: Liposomal Bupivacaine	Pain Scores: Control	Pain Scores: *P* Value	Opioid Consumption (mg): Morphine mg Equivalents	Opioid Consumption (mg): Liposomal Bupivacaine	Opioid Consumption (mg): Control	Opioid Consumption (mg): *P* Value	Length of Stay: Measure	Length of Stay: Liposomal Bupivacaine	Length of Stay: Control	Length of Stay: *P* Value	Reference
Statistically Significant Difference for Primary Outcome Measure															
Ankle open reduction internal fixation (n = 76)	Liposomal bupivacaine 266 mg (presumed) in 40 ml	Saline 40 ml	VAS at 24 h VAS at 48 h VAS at 72 h	6.4 5.1 4.0	7.4 6.5 5.7	< 0.05	Percocet tablets POD 1–3	9	11	0.12	Hours	121	92	*P* > 0.05	Davidovitch[93]
Hallux valgus osteotomy (n = 185)	Liposomal bupivacaine 120 In 8 ml	Saline 8 ml	No pain scores reported (outside of AUC 0–24 h)				"Adjusted mean total" number Percocet tablets	3.8	4.7	0.01	Not reported				Golf[94]
Hemorrhoidectomy (n = 186)	Liposomal bupivacaine 266* in 30 ml	Saline 30 ml	No pain scores reported (outside of AUC 0–72 h)				0–12 h 12–24 h 24–48 h 48–72 h	6.2 5.1 6.4 5.1	14.7 5.3 5.4 3.7	< 0.01 12–72 h not provided	Not reported (all subjects were required to remain hospitalized for a minimum of 72 h)				Gorfine[95]
Retropubic sling (n = 109)	Liposomal bupivacaine 266 in 30 ml	Saline 30 ml	VAS POD 1 VAS POD 2 VAS POD 3 VAS POD 4	1.0 1.4 0.6 0.3	2.7 1.7 1.0 0.6	0.01 0.19 0.01 0.34	POD 1 POD 2 POD 3 POD 4	6.6 6.0 5.6 3.8	7.0 5.0 4.7 4.3	0.295 0.01 0.24 0.64	Not reported				Mazloom-doost[96]
Laparotomy (n = 67)	Liposomal bupivacaine 266 in 200 ml†	No infiltration	Numeric Rating Scale POD 1 Numeric Rating Scale POD 2 Numeric Rating Scale POD 3	4.8 4.2 3.6	7.1 6.3 5.5	< 0.01	0–72 h	101	210	< 0.01	Days	9.3	10.4	0.41	Yalmanchili[97]

An additional publication (unregistered) reports adverse events from what appears to be an overlapping patient population,[205] and one study purports to be "randomized" but was actually sequential.[206] Primary outcomes are presented in table 1.
*Dose reported as 300 mg, but this is chemically equivalent to 266 mg free base, which is described by nearly all investigations.[23] †A third treatment group not involving infiltration excluded from this chart (*e.g.*, continuous peripheral nerve block).
AUC, area under the receiver operating characteristics curve; IV, intravenous; POD, postoperative day; VAS, visual analogue scale.

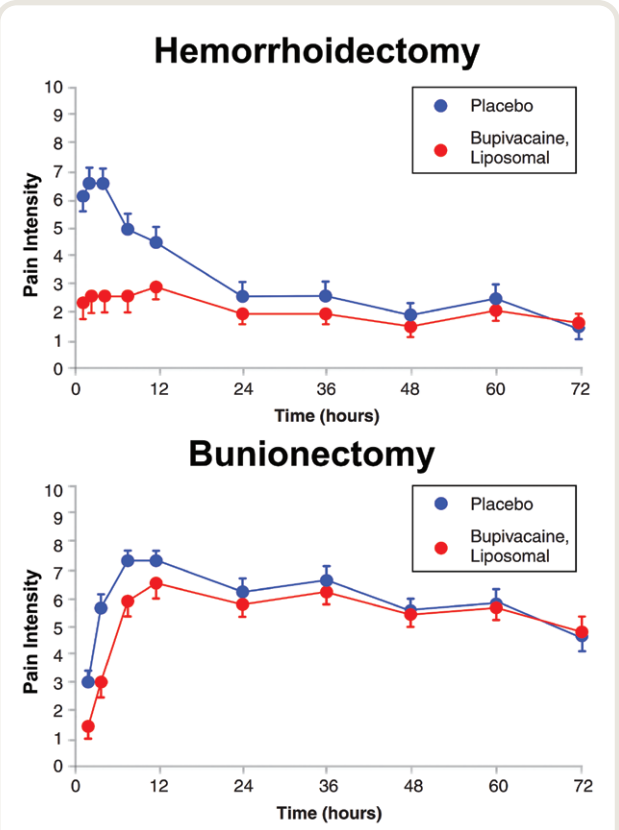

Fig. 1. Pain intensity *versus* time plot showing the difference in effect on mean ± SD pain with liposomal bupivacaine compared to placebo for (*A*) hemorrhoidectomy and (*B*) bunionectomy surgical site infiltration. Note that while the primary outcomes were the area under the curve for the first 72 and 48 h, respectively, and were positive for each, no differences were found at individual time points after 24 h. In other words, although liposomal bupivacaine was not found superior to placebo after the first 24 postoperative hours, the positive primary outcomes implied a duration of 48 to 72 h. Reproduced with permission, with color added for clarity.[100]

example, in a hypothetical study using this imputation technique, if a study subject has a pain score of 6 on the 0 to 10 scale and takes an opioid resulting in perfect analgesia for 6 h, the study reports this subject in moderate pain for the entire 6 h. However, this result would not accurately reflect the experience of patients outside of the randomized, controlled trial who would—again, hypothetically solely for illustration—experience moderate pain for the duration of analgesia onset, but then experience no pain for the remainder of the 6 h. This difficulty in interpreting imputed results may be partially alleviated if both the imputed and non-imputed scores are provided, or if the number of missing data points is provided. However, these two pivotal studies reported only the imputed values and no actual pain scores at any time point.[94,95]

Three additional randomized, controlled trials provide evidence of liposomal bupivacaine superiority over normal saline when infiltrated into the surgical site after a variety of orthopedic and soft tissue procedures, including ankle open reduction internal fixation,[93] retropubic sling placement,[96] and laparotomy,[97] although all had a high risk of bias with two failing to specify a primary outcome,[93,97] and the third demonstrating a discrepancy in primary outcome between the registry and published article.[96] Pain scores and opioid consumption were inconsistently improved at various time points within the first 72 postoperative hours, and the authors of one study questioned the cost–benefit ratio given the minimal benefit reflected in their results.[96] In contrast, seven other placebo-controlled randomized trials failed to detect a statistically significant difference between liposomal bupivacaine infiltration and normal saline for pain scores—usually the primary outcome—opioid consumption, and hospital length of stay.[86–92] Many of these studies involved surgical procedures similar to investigations reporting statistical significance, such as shoulder arthroplasty,[29,90] gynecologic surgery,[88,92,96] and cesarean delivery.[91,97]

Summary

To summarize the evidence for the use of surgical site infiltration with liposomal bupivacaine over normal saline, of the 12 published randomized, controlled trials, seven (58%) failed to find a statistically significant difference for the primary outcome measure; all but one with an overall low risk of bias.[86–92] In contrast, five of the 12 (42%) reported a statistically significance difference between active and placebo treatments for either the primary outcome measure or, for studies that did not predefine a specific primary outcome, most of the outcomes.[93–97] All five of these trials had an overall high risk of bias.[93–97] Results from the two pivotal placebo-controlled randomized trials suggest that liposomal bupivacaine infiltration results in decreased NRS after hemorrhoidectomy and hallux valgus osteotomy,[94,95] but the reporting of pain score data as AUC makes the actual duration of analgesia impossible to determine. Only with access to the primary data set could the Food and Drug Administration conclude that any analgesia improvements from liposomal bupivacaine were limited to only 24 h for hemorrhoidectomy and 12 h for hallux valgus osteotomy.[100] Furthermore, the imputation method used in both pivotal randomized, controlled trials exaggerates positive effects and decreases applicability to nonstudy patients.

Infiltration with Liposomal Bupivacaine *versus* an Active Control for Procedures other than Knee Arthroplasty

Long-acting local anesthetics, such as unencapsulated bupivacaine, have been clinically available for decades. For healthcare providers, the choice, therefore, is not between

liposomal bupivacaine and a placebo, but rather replacing an older medication with the new. Only studies including an active control can provide data on which to base a decision. Fortunately, at the time of this writing, there are 36 randomized, controlled trials involving surgical site infiltration comparing liposomal bupivacaine and unencapsulated bupivacaine or ropivacaine (tables 3-6).[23,31,102–131] Since nearly half of these include a single surgical procedure—knee arthroplasty—we will present these studies separately (tables 5 and 6).[23,31,117–131]

Of the 19 randomized, active-controlled trials involving surgical procedures other than knee arthroplasty, 15 (79%) failed to find a statistically significant difference for their primary outcome measure (tables 3 and 4).[23,102–112] These included both open and laparoscopic orthopedic and soft tissue procedures of the trunk, extremities, and dentition. While a few detected improvements favoring liposomal bupivacaine in some secondary endpoints,[102,103,105,109] the majority failed to detect statistically significant differences between treatments for all variables at all time points.[23,104,106–108,110–112] Overall risk of bias was deemed low in eight,[23,105–108,110] some concerns in three,[104,111,112] and high in three studies.[102,103,109] Multiple investigations were unregistered and/or did not specify a primary outcome measure time point, although the impact of these deficiencies appears minimal with the near total lack of statistical significance between treatments. Furthermore, some of the negative studies were phase II and III dose–response trials that were not specifically designed to investigate clinical effectiveness.[23] However, they were included in a manufacturer-supported review article that highlighted positive findings in various secondary and tertiary endpoints[23]; thus, it appears reasonable to include the negative findings here as well.

In contrast, 4 of the 19 randomized, controlled trials (21%) reported a statistically significant difference for their primary outcome measure(s) between liposomal bupivacaine and unencapsulated local anesthetic.[113–116] Three of these were rated as having a high risk of bias,[113,114,116] while one was rated as "some concerns."[115] The investigation with the strongest findings involved oral/dental implant surgery, with liposomal bupivacaine resulting in lower cumulative pain scores at all time points during the first postoperative week.[114] Satisfaction with analgesia was higher within the first 24 h after surgery, although there were no differences in opioid consumption.[114] Unfortunately, only 12.5 ml (63 mg) of bupivacaine hydrochloride was utilized for the comparison/control group—less than half of the 30 ml frequently used for simple molar extraction—while the maximum approved liposomal bupivacaine dose was utilized for the experimental group.[132] The registry provided no details as to how the primary outcome measure would be analyzed ("postsurgical pain severity [time frame: 7 days]"), and the published article did not mention a primary outcome measure (but stated that "no sample size calculation was performed"). Therefore, this trial was deemed to be at high risk of bias.[98,99]

Another randomized, controlled trial reporting a statistically significant difference for its primary outcome measure involved hemorrhoidectomy, which demonstrated liposomal bupivacaine benefits in pain scores, opioid consumption, and opioid-related side effects.[113] Pain scores were provided only in the cumulative 0 to 72 h AUC format, without daily totals, precluding assessment of the time window of true difference.[113] It is also noteworthy that comparing the maximum approved dose of liposomal bupivacaine (266 mg) to 75 mg of bupivacaine hydrochloride in this study resulted in a statistically significant difference; however, a very similar randomized, controlled trial that used a 100 mg bupivacaine hydrochloride dose did not detect a statistically significant difference between treatments.[23] Importantly, 100 mg still remains far below the maximum Food and Drug Administration–approved dose of bupivacaine hydrochloride—2.5 mg/kg up to 175 mg (3 mg/kg up to 225 mg with the addition of epinephrine)—while the maximum approved liposomal bupivacaine dose of 266 mg was utilized.[100] Due to a discrepancy between the registry description of the primary outcome measure and the published manuscript, this study was rated at high risk of bias.[98,99]

The remaining two investigations with statistically significant differences for their primary endpoints involved soft tissue surgical procedures.[115,116] The first examined infiltrating liposomal bupivacaine after midurethral sling placement and identified lower pain scores exclusively on the first postoperative day of seven.[115] The investigators concluded that liposomal bupivacaine "did not result in a *clinically significant* [emphasis added] difference in POD [postoperative day] 1 pain scores," and given the lack of analgesic improvement and opioid at other time points, "the cost of this anesthetic…may not justify its use…"[115] Similarly, while the authors of the second article found a statistically significant reduction in pain scores within the 72 h after mammoplasty, these improvements were less than 1.0 point on the 0 to 10 Numeric Rating Scale, leading the authors to conclude "that the additional cost of liposomal bupivacaine is unjustified for this particular use."[116]

Both of the two positive trials used a dose of bupivacaine hydrochloride for the control arm at less than half of the Food and Drug Administration–approved and frequently used maximum for these surgical procedures.[23,113,114,132] Both liposomal and unencapsulated bupivacaine have a dose–response relationship with increasing doses resulting in increased effects/duration and, conversely, decreasing dose resulting in decreased effects/duration.[23] Therefore, when evaluating active-controlled trials, lower dosing of the comparator local anesthetic reduces confidence in the clinical applicability of the results.

Table 3. Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Unencapsulated Ropivacaine, Bupivacaine, or Lidocaine for Surgical Procedures other than Knee Arthroplasty

	Treatments		Primary Outcome				Risks of Bias								
							Cochrane Risk of Bias 2								
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Radial fracture (n = 41)	Liposomal bupivacaine 133 mg in 10 ml bupivacaine HCl 50 mg in 20 ml	Bupivacaine hydrochloride 100 mg in 20 ml	13 primary outcome measures designated, all negative after day of surgery				-	-	+	+	+	?	Study funding; two authors with undisclosed general payments per Open Payments website	Not registered; randomization by day of birth (unconcealed); primary outcome designated both pain scores and pill counts without specifying time point(s)	Alter[102]
Laparoscopic hysterectomy (n = 64)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 50 mg in 20 ml	Average Numeric Rating Scale POD 1	4.2	5.0	> 0.05	-	+	+	+	+	-	None	Article presented average pain on POD 3 as the primary outcome; but it was prospectively designated as POD 1 in the registry (NCT02352922); authors concluded that results do "not validate its routine use in laparoscopic surgery"[103]	Barron[103]
Inguinal hernia repair (n = 76)	Liposomal bupivacaine 155–310 mg (volume not reported)	Bupivacaine hydrochloride 100 mg in 20 ml	Time to first supplemental pain medication use	Not reported		> 0.05	+	+	+	+	+	+	Study funding; author company employee	NCT01203644; phase II dose–response study; liposomal bupivacaine 310 mg treatment arm with dose greater than Food and Drug Administration–approved maximum of 266 mg	Bergese[23]
Inguinal hernia repair (n = 98)	Liposomal bupivacaine 93–306 mg (volume not reported)	Bupivacaine hydrochloride 105 mg (+ epinephrine) in 20 ml	Average Numeric Rating Scale AUC 0–72 h	Not reported		> 0.05	+	+	+	+	+	+	Study funding; author company employee	NCT00485433; phase II dose–response study; liposomal bupivacaine 306 mg treatment arm with dose greater than Food and Drug Administration–approved maximum of 266 mg	Bergese[23]

(*Continued*)

Table 3. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Breast augmentation (n = 80)	Liposomal bupivacaine 133 or 266 mg (volume not reported)	Bupivacaine hydrochloride 75 mg (+ epinephrine) in 15 ml	Average Numeric Rating Scale AUC 0–96 h	Not reported		> 0.05	+	+	+	+	+	+	Study funding; author company employee	NCT01206608; phase II dose–response study	Bergese[23]
Hemorrhoidectomy (n = 204)	Liposomal bupivacaine 266 mg (volume not reported)	Bupivacaine hydrochloride 100 mg (+ epinephrine) in 20 ml	Average Numeric Rating Scale AUC 0–96 h	Not reported		> 0.05	+	+	+	+	+	+	Study funding; author company employee	NCT00744848; phase III efficacy study	Bergese[23]
Orthopedic wrist surgery (n = 52)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 75 mg in 15 ml	Numeric Rating Scale POD 1	6.0	7.5	0.52	?	+	+	+	+	?	Product provided by company	Not registered; time point not specified for primary outcome, postoperative pain, but no time point detected a statistically significant difference	Dale[104]
			Numeric Rating Scale POD 2	3.5	3.0	0.42									
			Numeric Rating Scale POD 3	2.0	2.0	0.57									
			Numeric Rating Scale POD 4	2.0	2.0	0.14									
Total hip arthroplasty (n = 108)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg (+ epinephrine) in 120 ml	Ropiv 200–400 mg (+ epinephrine) in 120 ml	Maximum Numeric Rating Scale POD 1 06:00–12:00	3.0	4.0	0.10	+	+	+	+	+	+	Author paid consultant	Additional control group included in table 7; both treatments included ketorolac 30 mg	Johnson[105]
Laparoscopic urologic surgery (n = 191)	Liposomal bupivacaine 266 mg in 60 ml	Bupivacaine hydrochloride 2 mg/kg (maximum 150) mg in 60 ml	Morphine mg equivalent for entire hospitalization	15.0	17.3	0.39	+	+	+	+	+	+	None	Not registered	Knight[106]

(*Continued*)

Table 3. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Colon resection (n = 57)	Liposomal bupivacaine 266 mg in 30 ml	Bupivacaine hydrochloride 150 mg (+ epinephrine) in 30 ml	Morphine mg equivalent 0–48 h	15.0	12.8	0.54	+	+	+	+	+	+	None	Authors noted that "when excluding one outlier with length of stay 66 days, the mean is 4.0" *vs.* 6.2 reported in table 4 ($P = 0.79$).	Knudson[107]
Bariatric surgery (n = 179)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 150 mg in 100 ml	Bupivacaine hydrochloride 150 mg in 100 ml	Morphine mg equivalent for entire hospitalization	8.3	7.5	0.85	+	+	+	+	+	+	None	More control subjects were opioid-free on POD 2–4	Ma[108]
Breast reconstruction (n = 24)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 100 mg (+ epinephrine) in 20 ml	Average Numeric Rating Scale POD 1	3.7	3.7	> 0.05	-	+	+	-	?	-	None	Registration listed n = 200 and no interim analyses, but study ended with n = 24 due to "per protocol planned interim analysis"; no difference in pain scores yet 56% longer admission with bupivacaine hydrochloride and hospital "charges" 72% higher for bupivacaine hydrochloride subjects (P=0.04)	Motakef[109]
Hip arthroplasty (n = 107)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 80 ml	Bupivacaine hydrochloride 150 mg (+ epinephrine) in 60 ml	Morphine mg equivalent 0–72 h	100.3	121.2	0.25	+	+	+	+	+	+	Senior author paid consultant	Treatment group received 33% more volume than control group, possibly accounting for decreased opioid use for hours 0–12	Perets[110]

(*Continued*)

Table 3. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Anterior cruciate ligament reconstruction (n = 29)	Liposomal bupivacaine 266 mg in 40 ml	Bupivacaine hydrochloride 100 mg in 40 ml	Mean Numeric Rating Scale 24–36 h	5.6	5.2	0.69	?	+	+	+	+	?	Product donated	Primary outcome (pain scores) time point unclear between registration and manuscript, but all negative regardless; power analysis notes average Numeric Rating Scale 0–72 h	Premkumar[111]
			Mean Numeric Rating Scale 48–60 h	4.7	4.1	0.54									
			Mean Numeric Rating Scale 72–84 h	4.5	3.6	0.40									
Vaginal prolapse (n = 33)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 50 in 30 ml	Lido 150 mg in 30 ml	Median VAS 24 h	0	0	> 0.05	?	+	+	+	+	?	None	Primary outcome time point unclear between registration and manuscript, but all negative for VAS buttocks pain	Propst[112]
			Median VAS 48 h	0	0										
			Median VAS 72 h	0.2	0										
Statistically Significant Difference for Primary Outcome Measure															
Hemorrhoidectomy (n = 100)	Liposomal bupivacaine 66, 99, or 266 mg in 30 ml	Bupivacaine hydrochloride 75 mg in 30 ml	Average Numeric Rating Scale AUC 0–72 h liposomal bupivacaine 66 mg	220	335	> 0.05	-	+	+	+	+	-	Study funding; author company employee; no author conflict information	"*Post hoc* analysis" performed to include comparisons for different liposomal bupivacaine doses—the original analysis plan described in the registry did not divide the cohort by dose; daily pain scores not provided, so difficult to interpret clinical significance of the statistically significant difference in AUC	Haas[113]
			Average Numeric Rating Scale AUC 0–72 h liposomal bupivacaine 99 mg	165	335	< 0.01									
			Average Numeric Rating Scale AUC 0–72 h liposomal bupivacaine 266 mg	165	335	< 0.01									

(*Continued*)

Table 3. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Liposomal Bupivacaine	Control	*P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Dental implants (n = 69)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 63 mg in 32.6 ml	Bupivacaine hydrochloride 63 mg in 12.6 ml	Mandible Numeric Rating Scale Days 0–7	24.9	35.3	0.01	-	+	+	+	?	-	Study funding; first author paid consultant; author company employee	Volume of bupivacaine hydrochloride described as 7 "carpujects," equivalent to 12.6 ml (63 mg), or less than half of the 30 ml volume frequently used for molar extraction; investigators and outcome assessors were not masked to treatment group; in the registry, the time frame for the primary outcome ("postsurgical pain severity") was specified as "7 days" but no further details provided; the published article did not mention a primary outcome measure; mandible and maxilla pain separation not mentioned in registry (*post hoc* decision?); daily pain scores not provided—only cumulative sum of all scores to that time point—making it difficult to interpret clinical significance of the statistically significant differences	Iero[114]
			Maxilla Numeric Rating Scale Days 0–7	24.6	36.4	0.01									

(*Continued*)

Table 3. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Mid-urethral sling (n = 57)	Liposomal bupivacaine 266 mg in 60 ml	Bupivacaine hydrochloride 150 mg; lidocaine 500 mg in 100 ml	VAS POD 1	2.0	3.0	0.046	?	+	+	+	?	+	None	Outcome assessors possibly not masked to treatment group assignment; primary outcome statistically significant but did not reach prespecified clinical significance of 2; given the improved pain on only 1 day of 7, and no improvement in opioid use, the authors concluded liposomal bupivacaine did not result in "clinically significant differences"	Iwanoff[115]
Mammoplasty (n = 31)	Liposomal bupivacaine 130 mg (volume not reported)	Bupivacaine hydrochloride 130 mg (volume not reported)	24 primary outcome measures designated: most statistically significant				-	+	+	+	+	-	None	Not registered; split-body design with liposomal bupivacaine side randomized; 24 primary outcomes specified, all involving pain scores at various time points (0–72 h); the authors concluded "the difference in pain scores, although statistically significant, was small and likely clinically insignificant."	Nadeau[116]

An additional randomized trial compared infiltration with liposomal bupivacaine and bupivacaine hydrochloride for mammoplasty, but was excluded due to early termination by the manufacturer.[207] Secondary outcomes are presented in table 4; knee arthroplasty presented in tables 5 and 6.

*A third treatment group not involving infiltration excluded from chart (*e.g.*, continuous peripheral nerve block).

AUC, area under the receiver operating characteristics curve; VAS, visual analogue scale. Cochrane Risk of Bias 2 abbreviations: O, overall risk of bias; R, bias arising from the randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in selection of the reported result.

Table 4. Secondary Outcomes for Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Unencapsulated Ropivacaine, Bupivacaine, or Lidocaine for Surgical Procedures other than Knee Arthroplasty

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Radial fracture (n = 41)	Liposomal bupivacaine 133 mg in 10 ml bupivacaine hydrochloride 50 mg in 20 ml	Bupivacaine hydrochloride 100 mg in 20 ml	Numeric Rating Scale POD 0	4.0	6.0	< 0.05	POD 0–5	46	54	0.47		Not reported			Alter[102]
			Numeric Rating Scale POD 1	4.8	5.1	0.71									
			Numeric Rating Scale POD 2	5.3	3.8	0.07									
			Numeric Rating Scale POD 3	3.9	3.2	0.23									
Laparoscopic hysterectomy (n = 64)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 50 mg in 20 ml	Numeric Rating Scale POD 2	3.3	4.2	> 0.05	"Inpatient" POD 3	216	266	0.40	Hours	24	24	0.65	Barron[103]
			Numeric Rating Scale POD 3	2.8	4.1	0.02		320	344	0.89					
Inguinal hernia repair (n = 76)	Liposomal bupivacaine 155–310 mg (volume not reported)	Bupivacaine hydrochloride 100 mg in 20 ml	Numeric Rating Scale AUC 0–24 h	Not reported		< 0.05 for only 199 mg liposomal bupivacaine dose	0–24 h	Not reported		> 0.05		Not reported			Bergese[23]
			Numeric Rating Scale AUC 0–72 h	Not reported			0–72 h	Not reported							
Inguinal hernia repair (n = 98)	Liposomal bupivacaine 93–306 mg (volume not reported)	Bupivacaine hydrochloride 105 mg (+ epinephrine) in 20 ml	Numeric Rating Scale AUC 0–24 h	Not reported		> 0.05	0–24 h	Not reported		> 0.05		Not reported			Bergese[23]
			Numeric Rating Scale AUC 0–72 h	Not reported			0–72 h	Not reported							
Breast augmentation (n = 80)	Liposomal bupivacaine 133 or 266 mg (volume not reported)	Bupivacaine hydrochloride 75 mg (+ epinephrine) in 15 ml	Not reported				Not applicable (split-body trial with each subject receiving both treatments)					Not reported			Bergese[23]
Hemorrhoidectomy (n = 204)	Liposomal bupivacaine 266 mg (volume not reported)	Bupivacaine hydrochloride 100 mg (+ epinephrine) in 20 ml	Numeric Rating Scale AUC 0–24 h	Not reported		> 0.05	0–24 h	Not reported		> 0.05		Not reported			Bergese[23]
			Numeric Rating Scale AUC 0–72 h	Not reported			0–72 h	Not reported							

(*Continued*)

Table 4. (Continued)

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Orthopedic wrist surgery (n = 52)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 75 mg in 15 ml	Numeric Rating Scale POD 14	2.0	1.2	0.14	POD 1	8.0	10.0	0.10		Not reported			Dale[104]
							POD 2	7.7	4.5	0.87					
							POD 3	3.2	3.2	0.93					
							POD 4	2.3	2.4	0.80					
Total hip arthroplasty (n = 108)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg in 120 ml	Ropiv 200–400 mg in 120 ml	Maximum Numeric Rating Scale POD 0	4.0	4.0	0.80	POD 0	11.3	15.0	0.50	Days	2	2	0.77	Johnson[105]
			Maximum Numeric Rating Scale POD 1	4.0	5.5	0.01	POD 1	15.0	33.8	0.11					
			Maximum Numeric Rating Scale POD 2	3.5	5.0	0.02	POD 2	11.3	15.0	0.23					
Laparoscopic urologic surgery (n = 191)	Liposomal bupivacaine 266 mg in 60 ml	Bupivacaine hydrochloride 2 mg/kg (maximum 150) mg in 60 ml	Median Numeric Rating Scale during entire hospital stay	3.8	3.9	0.23	Entire hospital stay	18	19	0.39	Days	1	1	0.69	Knight[106]
Colon resection (n = 57)	Liposomal bupivacaine 266 mg in 30 ml	Bupivacaine hydrochloride 150 mg (+ epinephrine) in 30 ml	Numeric Rating Scale POD 4	6.3	5.3	0.08	Days 0–7	21.1	25.1	0.64	Days	4.1	6.2	0.62	Knudson[107]
Bariatric surgery (n = 179)	Liposomal bupivacaine 266 mg Bupivacaine hydrochloride 150 mg in 100 ml	Bupivacaine hydrochloride 150 mg in 100 ml	Numeric Rating Scale 0–24 h	8.0	7.5	0.13	0–24 h	8.0	7.5	0.94		Not reported			Ma[108]
			All hospital	8.3	7.5	0.21									
Breast reconstruction (n = 24)	Liposomal bupivacaine 266 mg in 20 ml	Bupivacaine hydrochloride 100 mg (+ epinephrine) in 20 ml	No secondary pain outcome measures reported				Morphine mg equivalent per hour	0.8	1.4	0.02	Hours	30	47	0.04	Motakef[109]
Hip arthroplasty (n = 107)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 80 ml	Bupivacaine hydrochloride 150 mg (+ epinephrine) in 60 ml	Mean VAS 0–72	3.8	3.7	0.64	0–12 h	35	51	0.03	Hours	46	44	0.45	Perets[110]
							12–24 h	38	30	0.90					
							24–36 h	17	21	0.49					

(*Continued*)

Table 4. (Continued)

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Anterior cruciate ligament reconstruction (n = 29)	Liposomal bupivacaine 266 mg in 40 ml	Bupivacaine hydrochloride 100 mg in 40 ml	Mean Numeric Rating Scale 36–48 h	4.9	5.1	0.87	0–144 h	77	64	0.20	Minutes (in recovery room)	106	108	0.85	Premkumar[111]
			Mean Numeric Rating Scale 60–72 h	4.8	3.7	0.22									
			Mean Numeric Rating Scale 84–96 h	4.1	3.3	0.39									
Vaginal prolapse (n = 33)	Liposomal bupivacaine 266; bupivacaine hydrochloride 50 in 30 ml	Lidocaine 150 mg in 30 ml	Median VAS 96 h	0	2.0	> 0.05	All hospital	12	15	0.84		Not reported		> 0.05	Propst[112]
					1.0		At Day 4	12	15	0.59					
			Median VAS 120 h	0											
			Statistically Significant Difference for Primary Outcome Measure												
Hemorrhoidectomy (n = 100)	Liposomal bupivacaine 66, 99, or 266 mg in 30 ml	Bupivacaine hydrochloride 75 mg in 30 ml	Pain scores at individual time points not reported				24 h liposomal bupivacaine 66 mg	17	13	> 0.05	Hours	Not reported		> 0.05	Haas[113]
							24 h liposomal bupivacaine 99 mg	11	13	> 0.05					
							24 h liposomal bupivacaine 266 mg	8	13	< 0.05					
Dental implants (n = 69)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 63 mg; lidocaine 800 mg (+ epinephrine) in 72.6 ml	Bupivacaine hydrochloride 63 mg; lidocaine 800 mg (+ epinephrine) in 52.6 ml	Pain scores at individual time points not reported				Oxycodone use	Not reported		> 0.05		Not reported			Iero[114]
Mid-urethral sling (n = 57)	Liposomal bupivacaine 266 mg in 60 ml	Bupivacaine hydrochloride 150 mg; lidocaine 500 mg in 100 ml	VAS POD 2	2.0	2.0	0.58	POD 0–7	0	0	0.83		Not reported			Iwanoff[115]
			VAS POD 3	2.0	2.0	0.78									
			VAS POD 4	0	1.5	0.92									
Mammoplasty (n = 31)	Liposomal bupivacaine 130 mg (volume not reported)	Bupivacaine hydrochloride 130 mg (volume not reported)	No secondary pain score outcomes reported					Not reported				Not reported			Nadeau[116]

An additional randomized trial compared infiltration with liposomal bupivacaine and bupivacaine hydrochloride for mammoplasty but was excluded due to early termination by the manufacturer.[207] Primary outcomes are presented in table 3; knee arthroplasty presented in tables 5 and 6.

*A third treatment group not involving infiltration excluded from chart (*e.g.*, continuous peripheral nerve block).

AUC, area under the curve; POD, postoperative day; VAS, visual analogue scale.

Summary

To summarize the evidence for the use of infiltration with liposomal bupivacaine over unencapsulated bupivacaine, of the 19 randomized, active-controlled trials (excluding knee arthroplasty), only two (11%) reported both a statistically and clinically significant difference for their primary outcome measure.[113,114] Both of these trials compared the maximum approved dose of liposomal bupivacaine (266 mg) to submaximal doses of the unencapsulated bupivacaine comparator.[113,114] This discrepancy greatly decreases confidence that the difference would remain had a maximum dose of both treatments been compared.[113] Furthermore, both trials were rated at high risk of bias for multiple reasons, the most critical being discrepancies between the registry entries and published articles involving the primary outcome measures. Therefore, there is currently no published evidence with a low risk of bias for surgical procedures other than knee arthroplasty demonstrating that infiltration with the maximum approved liposomal bupivacaine dose is superior to unencapsulated bupivacaine to a statistically and clinically significant degree.

Infiltration with Liposomal Bupivacaine *versus* an Active Control for Knee Arthroplasty

Knee arthroplasty is among the most common and painful surgical procedures, with more than 700,000 performed annually within the United States alone. Infiltrating the surgical site with local anesthetic is frequently performed by surgeons to provide postoperative analgesia, although the duration of effect is far less than the duration of surgically related pain.

Of the 17 randomized, active-controlled trials involving knee arthroplasty, 15 (88%) failed to find a statistically significant difference for their primary outcome measure (tables 5 and 6).[23,31,117–129] Risk of bias for these 15 trials was deemed low in eight studies[23,31,119,122–124,126,127] and "some concerns" in seven trials.[117,118,120,121,125,128,129] Within these studies, differences between treatments for nearly every secondary endpoint involving pain level, opioid use, physical therapy, or discharge day also failed to reach statistical significance. Nearly no statistically significant differences between infiltration with liposomal bupivacaine and unencapsulated bupivacaine after total knee arthroplasty were identified. Of the few exceptions, the unencapsulated local anesthetic control was found superior to liposomal bupivacaine[118,126–128] more times than *vice versa*.[119] Multiple investigations were unregistered and/or did not specify a primary outcome measure time point, although the impact of these deficiencies appears minimal with the near-total lack of statistical significance between treatments. A unique and illuminating investigation randomized each side of subjects having bilateral knee arthroplasty (n = 29) to either a combination of liposomal bupivacaine (266 mg) and bupivacaine hydrochloride (75 mg) or ropivacaine hydrochloride (250 mg) plus epinephrine, ketorolac, and clonidine.[121] This split-body study design is especially powerful since it inherently controls for intersubject differences in pain evaluation and supplemental opioid consumption between treatment groups (each subject receives both treatments, and therefore each treatment is associated with identical opioid doses). No statistically significant or clinically relevant (defined by the authors as greater than 18 mm on the 0 to 100 mm visual analogue scale [VAS]) differences between treatments were detected, mirroring the vast majority of published trials (tables 5 and 6).

In contrast, two of the 17 randomized, controlled trials (12%) reported a statistically significant difference for their primary outcome measure(s) between liposomal bupivacaine and unencapsulated local anesthetic.[130,131] The first randomized subjects (n = 70) to either a maximum dose of liposomal bupivacaine (266 mg) or a multicomponent injection of ropivacaine (400 mg), ketorolac, morphine, and epinephrine.[131] Considering the Food and Drug Administration–recommended maximum dose of ropivacaine (with epinephrine) is 4 mg/kg up to 225 mg, an optimized control group was certainly provided with 400 mg used in this study. Statistically significant differences were identified not only for the primary outcome of pain level on postoperative day 1 but also in pain scores within the recovery room and postoperative day 2. Differences were also detected in opioid consumption in the recovery room and postoperative days 1 and 2, and the risk of bias was evaluated as low using the Cochrane risk-of-bias tool.[98,99]

The second randomized, controlled trial, the PILLAR trial, randomized subjects (n = 140) to infiltration with either a combination of liposomal (266 mg) and unencapsulated (100 mg) bupivacaine, or solely bupivacaine hydrochloride (100 mg).[130] The results of this investigation were overwhelmingly positive not only for the two coprimary outcomes of pain scores (AUC, 12 to 48 h) and opioid consumption (cumulative, 0 to 48 h),[133] but also for secondary and tertiary endpoints at 24, 48, and 72 h.[130,133,134] For example, mean total opioid consumption in the first 48 h postsurgery was 16 *versus* 80 mg for the experimental *versus* control groups, respectively ($P = 0.0029$).[133] More subjects receiving liposomal bupivacaine remained opioid-free, exhibited a greater amount of time until request for first opioid rescue, were more satisfied with postoperative analgesia, and met discharge criteria earlier than in the control group.[130,133,134]

The authors attribute their dramatically different results compared to most other randomized, active-controlled trials to their use of a large volume of injectate (120 ml);[135] the "use of a small-bore (22-gauge), 1.5-inch needle to reduce the leakage of anesthetic solution from the injection site and for achievement of maximal tissue exposure"[135–137]; and their "use of a meticulous and standardized infiltration protocol."[130,138] This protocol entailed the use of six 20-ml syringes of study fluid with 94 to 103 separate needle passes/injections.[130,135] However, six of the trials that did not

Table 5. Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Unencapsulated Ropivacaine, Bupivacaine, or Lidocaine for Knee Arthroplasty

	Treatments		Primary Outcome				Risks of Bias								
							Cochrane Risk of Bias 2								
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Knee arthroplasty (n = 162)	Liposomal bupivacaine 266 mg (+ epinephrine) in 60 ml	Bupivacaine hydrochloride 50 mg (+ epinephrine) in 60 ml	30 primary outcome measures designated but no outcome was statistically significant				?	+	+	+	+	?	None	Primary outcome of registry is VAS "within first 30 days postoperatively" but in manuscript is VAS "within 96 hours after surgery," without specifying worst, average, or least daily pain	Alijanipour[117]
Knee arthroplasty (n = 107)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg (+ epinephrine) in 120 ml	Ropiv* 200–400 mg (+ epinephrine) in 120 ml	Median maximum Numeric Rating Scale POD 1 06:00–12:00	4.5	4.0	0.196	?	+	+	+	?	+	Author paid consultant	Additional treatment group included in table 7; both groups included ketorolac 30 mg; data collectors not masked to treatment group	Amundson[118]
Knee arthroplasty (n = 78)	Liposomal bupivacaine 266 mg + bupivacaine hydrochloride 125 mg (+ epinephrine) in 60 ml	Ropiv* 250 mg (+ epinephrine) in 60 ml	Median VAS POD 1	1	2	0.127	+	+	+	+	+	+	Multiple authors paid consultants	Not registered; additional control group with intrathecal opioids excluded*; both groups included ketorolac 30 mg	Barrington[119]
Knee arthroplasty (n = 245)	Liposomal bupivacaine 532 mg in 40 ml	Bupivacaine hydrochloride 200 mg (+ epinephrine) in 40 ml	Average Numeric Rating Scale AUC 0–72 h	Not reported		> 0.05	+	+	+	+	+	+	Study funding; author company employee	Liposomal bupivacaine group received twice current Food and Drug Administration–approved maximum dose; phase III clinical trial	Bergese[23]

(*Continued*)

Table 5. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Knee arthroplasty (n = 138)	Liposomal bupivacaine 133–266 mg in 60 ml	Bupivacaine hydrochloride 150 mg in 60 ml	Average Numeric Rating Scale AUC 0–96 h Liposomal bupivacaine 133 mg	21	19	> 0.05	+	+	+	+	+	+	Study funding; author company employee	Phase II dose-ranging study; two doses of liposomal bupivacaine over 266 mg approved maximum not included	Bramlett[31]
			Average Numeric Rating Scale AUC 0–96 h liposomal bupivacaine 266 mg	20	19	> 0.05									
Knee arthroplasty (n = 138)	Liposomal bupivacaine 266 mg in 60 ml	Ropiv 246 mg (+ epinephrine) in 60 ml	No primary outcome specified, but no outcome was statistically significant				?	+	+	+	+	?	None	Not registered; no primary outcome defined, but all outcomes negative; control group also received ketorolac (30 mg) and clonidine 0.08 mg with ropivacaine/epinephrine	Collis[120]
Knee arthroplasty (n = 29)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 100 ml	Ropiv 250 mg (+ epinephrine) in 100 ml	"VAS pain scores" but no time point specified, but no outcome was statistically significant				?	+	+	+	+	?	None	Not registered; primary outcome was "VAS pain scores" but time point left undefined, but all negative; bilateral surgery and split-body design: each knee assigned one of the two treatments	Danoff[121]

(*Continued*)

Table 5. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Knee arthroplasty (n = 96)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride† (+ epinephrine) in 100 ml	Ropiv † (+ epinephrine) in 100 ml	VAS POD 1	4.1	3.4	> 0.05	+	+	+	+	+	+	None	Not registered; doses of bupivacaine hydrochloride and ropiv not provided; both treatments also included unknown doses of ketorolac and morphine	DeClaire[122]
			VAS POD 2	4.4	4.6										
			Hydrocodone POD 1 and 2	98	90										
Knee arthroplasty (n = 59)	Liposomal bupivacaine 266 mg in 60 ml	Ropiv 40 in 60 ml	Number of therapy sessions until discharge	3.0	3.6	0.14	+	+	+	+	+	+	Unclear	Not registered; adductor canal nerve block for both treatment groups (20 ml ropiv 0.5%); ropiv treatment included 10 mg morphine, 30 mg ketorolac, and 40 mg methylprednisolone	Hyland[123]
Knee arthroplasty (n = 125)	Liposomal bupivacaine 266 mg (presumed) in 60 ml	Bupivacaine hydrochloride 75 mg (+ epinephrine); morphine 10 mg in 60 ml*	Mean Numeric Rating Scale POD 1	3.9	4.0	0.94	+	+	+	+	+	+	None	Not registered; liposomal bupivacaine dose unspecified; additional control group with intra-articular injection instead of infiltration excluded*	Jain[124]
Knee arthroplasty (n = 111)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 50 ml	Bupivacaine hydrochloride 150 mg in 60 ml	"VAS pain scores" but no time point specified, but no outcome was statistically significant				?	+	+	+	+	?	None	Not registered; primary outcome time point undefined, but all negative; authors noted, "sales representatives of Exparel were invited to educate surgeon and staff on optimal use of the study medication"	Schroer[125]

(*Continued*)

Table 5. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Knee arthroplasty (n = 110)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 1 mg/kg in 60 ml	Bupivacaine hydrochloride* 1 mg/kg in 60 ml	Hospital length of stay (days)	1.9	1.8	0.37	+	+	+	+	+	+	None	Not registered; additional control group with intrathecal opioids excluded*	Schumer[126]
Knee arthroplasty (n = 38)	Liposomal bupivacaine 266 mg Bupivacaine hydrochloride 50 mg in 100 ml	Ropiv 246 mg (+ epinephrine) in 100 ml	Total opioid morphine mg equivalent	Not reported		0.33	+	+	+	+	+	+	None	Article states registered, but no identifier provided, and a search failed to locate; enrolled exclusively opioid-dependent patients; control group included clonidine and ketorolac	Schwarzkopf[127]
Knee arthroplasty (n = 104)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 100 ml	Bupivacaine hydrochloride 75 mg; lidocaine 150 mg (+ epinephrine) in 98 ml*	Primary outcomes listed as VAS, total morphine mg equivalent, and opioid-related symptom distress scale at 24 and 48 h (but all either not statistically significant or the control was superior to liposomal bupivacaine)				?	+	+	+	+	?	None	Not registered; control treatment also included 10 mg morphine and 60 mg ketorolac; multiple primary outcomes measures and time points specified	Suarez[128]
Knee arthroplasty (n = 78)	Liposomal bupivacaine 266 mg in 90 ml	Bupivacaine hydrochloride 100 mg in 90 ml*	No primary outcome measure was specified, but no outcome was statistically significant with the preplanned Bonferroni correction				?	+	+	+	+	?	None	Not registered; no primary outcome specified; liposomal bupivacaine reported lower pain POD 1 during therapy but not statistically significant with planned Bonferroni correction	Zlotnicki[129]

(*Continued*)

Table 5. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Statistically Significant Difference for Primary Outcome Measure															
Knee arthroplasty (n = 140)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 120 ml	Bupivacaine hydrochloride 100 mg in 120 ml	VAS AUC 12–48 h	209	181	0.04	-	+	+	?	+	-	Company provided funding and "participated in the study conception and design; collection, analysis, and interpretation of the data; and review of the manuscript"[113]; four of five authors paid consultants; author with company stock or stock options	Pain outcomes calculated with last observation carried forward with rescue analgesic; the original, published statistical plan was not applied[135]; if it had been applied, neither primary outcome measure would have reached statistical significance[140]; original, published protocol described many secondary outcome measures that were not presented in the final manuscript (or registry); many secondary outcomes described in manuscript that were not included in registry	Mont[130,133–135]
			Total morphine mg equivalent 0–48 h	19	85	< 0.01									
Knee arthroplasty (n = 70)	Liposomal bupivacaine 266 mg in 100 ml	Ropiv 400 mg (+ epinephrine) in 100 ml	Mean Numeric Rating Scale POD 1	2.6	3.3	0.02	+	+	+	+	+	+	None	Control treatment also included 30 mg ketorolac, and 5 mg morphine; primary outcome measure not noted in manuscript but included in registry entry	Snyder[131]

One randomized trial compared infiltration and a peripheral nerve block, both with liposomal bupivacaine and is therefore presented in table 9.[16] Secondary outcomes are presented in table 6.

*A third control group not involving peripheral nerve blocks excluded from chart (*e.g.*, unencapsulated bupivacaine infiltration).[145] † Dosage unknown.

AUC, area under the curve; VAS, visual analogue scale. Cochrane Risk of Bias 2 abbreviations: O, overall risk of bias; R, bias arising from the randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in selection of the reported result.

Table 6. Secondary Outcomes for Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Unencapsulated Ropivacaine, Bupivacaine, or Lidocaine for Knee Arthroplasty

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
No Statistically Significant Difference for Primary Outcome Measure															
Knee arthroplasty (n = 162)	Liposomal bupivacaine 266 mg (+ epinephrine) in 60 ml	Bupivacaine hydrochloride 50 mg (+ epinephrine) in 60 ml	No secondary pain outcomes reported				POD 0–3	102	96	> 0.05		Not reported			Alijanipour[117]
Knee arthroplasty (n = 107)	Liposomal bupivacaine 266 mg + bupivacaine hydrochloride 125 mg (+ epinephrine) in 120 ml	Ropiv* 200–400 mg (+ epinephrine) in 120 ml	Average Numeric Rating Scale POD 0	2.4	1.7	0.02	POD 0	15	8	0.29	Days	2	2	0.77	Amundson[118]
			Average Numeric Rating Scale POD 1	3.7	3.5	0.21	POD 1	45	38	0.15					
			Average Numeric Rating Scale POD 2	3.5	3.2	0.13	POD 2	23	15	0.13					
Knee arthroplasty (n = 78)	Liposomal bupivacaine 266 mg + bupivacaine hydrochloride 125 mg (+ epinephrine) in 60 ml	Ropiv* 250 mg (+ epinephrine) in 60 ml	Median VAS 12 h	0	3	< 0.01	Total Mean	71	75	0.91	Days	1.8	1.8	0.82	Barrington[119]
			Median VAS POD 2	4	4	0.85	Total Median	40	70	0.15					
			Median VAS POD 3	4	3	0.72									
Knee arthroplasty (n = 245)	Liposomal bupivacaine 532 mg in 40 ml	Bupivacaine hydrochloride 200 mg in 40 ml	Numeric Rating Scale AUC 0–24 h	Not reported		> 0.05		Not reported				Not reported			Bergese[23]
			Numeric Rating Scale AUC 0–72 h												
Knee arthroplasty (n = 138)	Liposomal bupivacaine 133–266 mg in 60 ml	Bupivacaine hydrochloride 150 mg in 60 ml	Mean Numeric Rating Scale liposomal bupivacaine 266 mg POD 1	3.1	4.3	> 0.05		Not reported				Not reported			Bramlett[31]
			Mean Numeric Rating Scale liposomal bupivacaine 266 mg POD 2	4.7	4.8	> 0.05									

(*Continued*)

Table 6. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Pain Scores: Measure	Pain Scores: Liposomal Bupivacaine	Pain Scores: Control	Pain Scores: *P* Value	Opioid Consumption (mg): Morphine mg Equivalents	Opioid Consumption (mg): Liposomal Bupivacaine	Opioid Consumption (mg): Control	Opioid Consumption (mg): *P* Value	Length of Stay: Measure	Length of Stay: Liposomal Bupivacaine	Length of Stay: Control	Length of Stay: *P* Value	Reference
Knee arthroplasty (n = 138)	Liposomal bupivacaine 266 mg in 60 ml	Ropiv 246 mg (+ epinephrine) in 60 ml	Mean Numeric Rating Scale 24 h	5.3	5.3	> 0.05	Hydrocodone (mg) 24 h	142	121	> 0.05	Days	3.1	2.8	0.14	Collis[120]
			Mean Numeric Rating Scale 48 h	5.0	5.0		Hydrocodone (mg) 48 h	125	135						
			Mean Numeric Rating Scale 72 h	4.4	4.3		Hydrocodone (mg) 72 h	84	87						
Knee arthroplasty (n = 29)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 100 ml	Ropiv 250 mg (+ epinephrine) in 100 ml	All pain scores defined as primary outcomes, but no outcome was statistically significant				Not applicable as each subject received both treatments—one in each knee				Not applicable as each subject received both treatments—one in each knee				Danoff[121]
Knee arthroplasty (n = 96)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride† (+ epinephrine) in 100 ml	Ropiv† (+ epinephrine) in 100 ml	All pain scores defined as primary outcomes, but no outcome was statistically significant				All opioid consumption incorporated into primary outcome measure				Hours	59	60	0.98	DeClaire[122]
Knee arthroplasty (n = 59)	Liposomal bupivacaine 266 mg in 60 ml	Ropiv 40 in 60 ml	Average Numeric Rating Scale	4.4	4.7	0.34	Total	275	305	0.39	Days	2.5	2.3	0.21	Hyland[123]
Knee arthroplasty (n = 125)	Liposomal bupivacaine 266 mg (presumed) in 60 ml	Bupivacaine hydrochloride 75 mg (+ epinephrine); morphine 10 mg in 60 ml*	Maximum Numeric Rating Scale	5.7	5.8	0.92	Morphine mg equivalent per 24 h	99	100	0.97		Not reported		> 0.05	Jain[124]
Knee arthroplasty (n = 111)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 50 ml	Bupivacaine hydrochloride 150 mg in 60 ml	All pain scores defined as primary outcomes, but no outcome was statistically significant				Total	54	52	0.34	Days	2.9	3.0	0.98	Schroer[125]
Knee arthroplasty (n = 110)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 1 mg/kg in 60 ml	Bupivacaine hydrochloride*1 mg/kg in 60 ml	Mean daily Numeric Rating Scale	3.7	3.6	0.70	Mean daily	68	77	> 0.05		Not reported			Schumer[126]
Knee arthroplasty (n = 38)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 50 mg in 100 ml	Ropiv 246 mg (+ epinephrine) in 100 ml	Median VAS POD 1	6.0	7.0	> 0.05	Total POD 1	102	100	> 0.05		Not reported		> 0.05	Schwarzkopf[127]
			Median VAS POD 2	5.2	5.0	> 0.05	Total POD 2	60	35	> 0.05					

(*Continued*)

Table 6. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Pain Scores: Measure	Pain Scores: Liposomal Bupivacaine	Pain Scores: Control	Pain Scores: *P* Value	Opioid Consumption (mg): Morphine mg Equivalents	Opioid Consumption (mg): Liposomal Bupivacaine	Opioid Consumption (mg): Control	Opioid Consumption (mg): *P* Value	Length of Stay: Measure	Length of Stay: Liposomal Bupivacaine	Length of Stay: Control	Length of Stay: *P* Value	Reference
Knee arthroplasty (n = 104)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 100 ml	Bupivacaine hydrochloride 75 mg; lidocaine 150 mg (+ epinephrine) in 98 ml*	All pain scores defined as primary outcomes, but no outcome was statistically significant				All opioid defined as primary outcomes, but no time point was statistically significant				Days	2.0	1.8	0.19	Suarez[128]
Knee arthroplasty (n = 78)	Liposomal bupivacaine 266 mg in 90 ml	Bupivacaine hydrochloride 100 mg in 90 ml*	Numeric Rating Scale during physical therapy POD 1	5.4	6.9	0.03	Mean 0–24 h	40	42	> 0.05		Not reported			Zlotnicki[129]
			Numeric Rating Scale during physical therapy POD 2	3.9	5.0	0.17	Mean 24–48 h	61	54						
							Mean 48–72 h	41	34						
Statistically Significant Difference for Primary Outcome Measure															
Knee arthroplasty (n = 140)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 120 ml	Bupivacaine hydrochloride 100 mg in 120 ml	No pain scores for specific time points provided–solely VAS AUC for hours 12-48 as part of the primary outcome. No pain scores for hours 48-72 as well even though opioid data collected during this time period.				0–72 h	21	94	0.01	Not reported (although registry entry states that length of stay would be a secondary outcome)[140]				Mont[130,133–135]
Knee arthroplasty (n = 70)	Liposomal bupivacaine 266 mg in 100 ml	Ropiv 400 mg (+ epinephrine) in 100 ml	Mean Numeric Rating Scale POD 2	2.4	3.5	< 0.01	POD 1	10.9	15.6	0.8		Not reported			Snyder[131]
							POD 2	6.9	13.1	< 0.01					

An additional randomized trial compared infiltration with liposomal bupivacaine and bupivacaine hydrochloride for mammoplasty but was excluded due to early termination by the manufacturer.[207] Primary outcomes are presented in table 5.

*A third treatment group not involving infiltration excluded from chart (*e.g.*, continuous peripheral nerve block). †Dosage unknown.

AUC, area under the receiver operating characteristics curve; POD, postoperative day; VAS, visual analogue scale.

detect statistically significant differences in their primary outcome measure(s) employed similarly high injection volumes of 90 to 120 ml,[118,121,122,127–129] and a seventh described administering "approximately 50 injections," although the total volume was not specified.[119] In addition, authors of many of the trials without statistically significant findings describe an involved infiltration protocol very similar to the PILLAR technique, including one group of authors who pointedly noted that "the collaborating surgeon received extensive printed and in-person education on appropriate installation technique as recommended by the manufacturer before study initiation, and a drug manufacturer representative was present in the operating room to provide support on proper drug administration as needed for the first study patients."[123]

An additional possible difference among studies accounting for the vastly dissimilar analgesic findings might be that the PILLAR trial was unique in applying the windowed worst-observation-carried-forward method, specifying that "pain intensity scores during periods of rescue medication administration were *replaced* by the *highest* observed score before rescue medication use" [emphasis added].[130] The results without the "window" adjustments were not provided—unlike other manufacturer-supported randomized, controlled trials[29,139]—so it remains unknown whether the relatively small difference in pain scores between treatments (approximately 180 *vs.* 207 AUC during 36 h; $P = 0.038$) would have remained statistically significant without replacing the lower with higher scores. The authors had published their protocol—including details of the statistical plan—before beginning enrollment,[135] but the windowed technique was not mentioned in that publication or the clinicaltrials.gov registry (NCT02713490). More importantly, the ultimate statistical analysis deviated from the prespecified statistical plan in three critical aspects, and if the original plan had been adhered to, the primary outcome measures would not have reached statistical significance, even with the "window" imputation.[140] These two factors resulted in a high risk of bias using the Cochrane tool.[98,99] Last, while for the experimental group the maximum Food and Drug Administration–approved liposomal bupivacaine (266 mg) combined with an additional 100 mg of bupivacaine hydrochloride was employed, the control group received only 57% of the possible maximum unencapsulated bupivacaine dose, and without epinephrine, which is commonly included to increase both the maximum dose (to 225 mg) and duration of effect.

Summary

To summarize the evidence for the use of infiltration with liposomal bupivacaine over unencapsulated bupivacaine during knee arthroplasty, of the 17 available randomized, active-controlled trials, only two (12%) reported a statistically significant difference for their primary outcome measure(s),[130,131] with the remainder observing few if any statistically significant differences in secondary and tertiary endpoints (tables 5 and 6).[23,31,117–129] For one of the two trials with statistically significant findings,[130] deviation from the published prespecified statistical plan resulted in a positive outcome when adherence to the original design would have rendered neither of the two coprimary endpoints statistically significant.[140] In addition, this study used a submaximal dose of unencapsulated bupivacaine for the comparison group, while subjects of the treatment group received the maximum approved dose of liposomal bupivacaine plus additional bupivacaine hydrochloride.[130] This discrepancy greatly decreases confidence that the statistically significant differences would remain had a maximum dose of both treatments been compared.[130] Consequently, there is currently little published evidence with a low risk of bias demonstrating that administration of the maximum approved liposomal bupivacaine dose is superior to unencapsulated bupivacaine hydrochloride when surgically infiltrated for knee arthroplasty.

Infiltration with Liposomal Bupivacaine *versus* a Peripheral Nerve Block with Unencapsulated Long-acting Local Anesthetic

Single-injection Peripheral Nerve Block

A single-injection peripheral nerve block using the longest acting local anesthetic approved in the United States, bupivacaine hydrochloride, provides a sensory and motor block with a typical duration of 8 to 12 h, although a longer period may occur depending on the anatomic location, inclusion of additives, and other factors. Regardless, nearly all bupivacaine hydrochloride–based regional anesthetics resolve in less than 24 h. Since peripheral nerve blocks require additional equipment (*e.g.*, ultrasound), expertise, and time to administer, surgical infiltration of a sustained released local anesthetic may be a useful alternative if found to deliver at least equivalent analgesia.

Eleven randomized, controlled trials compare a single-injection peripheral nerve block of unencapsulated long-acting local anesthetic with surgical infiltration of liposomal bupivacaine (tables 7 and 8).[90,105,118,141–148] Of the eight that involve shoulder and knee procedures,[90,118,141–146] all were deemed to have some concerns regarding bias due mainly to a lack of treatment group masking. All either had an inadequately defined primary outcome measure or used a primary outcome that included a longer duration than anticipated for the unencapsulated local anesthetic peripheral nerve block (greater than 12 h).[90,118,141–146] However, the secondary outcomes allow a comparison of liposomal bupivacaine infiltration and peripheral nerve blocks. All eight reported statistically significant and clinically relevant improvements in pain scores in favor of the peripheral nerve block during the anticipated duration of the block (8 to 12 h). Of these, half also found that the peripheral nerve

Table 7. Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Peripheral Nerve Blocks with Unencapsulated Bupivacaine or Ropivacaine

	Treatments		Primary Outcome				Risks of Bias								
							Cochrane Risk of Bias 2								
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Single-injection Peripheral Nerve Block vs. Liposomal Bupivacaine Infiltration (Knee and Shoulder Surgery)															
Shoulder arthroplasty (n = 156)	Liposomal bupivacaine 266 mg in 40 ml	Interscalene nerve block: ropiv 150 mg in 30 ml	Morphine mg equivalent 0–24 h	15	15	0.85	?	+	+	+	?	+	None	Subjects and outcome assessors not masked to treatment group assignment	Namdari[90]
Anterior cruciate ligament reconstruction (n = 82)	Liposomal bupivacaine 266 mg in 30 ml	Femoral nerve block: ropiv 200 mg in 40 ml	Mean daily VAS	Not reported		> 0.05	?	+	+	+	?	+	None	Subjects and outcome assessors not masked to treatment group assignment	Okoroha[141]
Total shoulder arthroplasty (n = 57)	Liposomal bupivacaine 266 mg in 40 ml	Interscalene nerve block: ropiv 200 mg in 40 ml	Mean daily VAS	Not reported		> 0.05	?	+	+	+	?	+	None	Subjects and outcome assessors not masked to treatment group assignment	Okoroha[142]
Knee arthroplasty (n = 80)	Liposomal bupivacaine 266 mg in 60 ml	Femoral nerve block: ropiv 200 mg (+ epinephrine) in 50 ml	Mean Numeric Rating Scale during hospitalization	3.4	2.9	0.07	?	+	+	+	?	+	None	Not registered; control treatment included 30 mg of tetracaine; subjects and outcome assessors not masked to treatment group assignment	Surdam[143]
Knee arthroplasty (n = 373)	Liposomal bupivacaine 266 mg bupivacaine hydrochloride 75 mg in	Femoral nerve block: bupivacaine hydrochloride 50 mg in 20 ml infiltration; bupivacaine hydrochloride 75 in 30 ml	Primary outcome measure undefined, but power analysis indicated time point was 1 yr after surgery				?	+	+	+	+	?	None	Not registered; liposomal bupivacaine group received a saline femoral nerve block to retain masking to treatment assignment; control group received bupivacaine infiltration to only the posterior capsule	Talmo[144]

(*Continued*)

Table 7. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Single-injection and/or Continuous Peripheral Nerve Block vs. Liposomal Bupivacaine Infiltration (Knee and Shoulder Surgery)															
Total shoulder arthroplasty (n = 83)	Liposomal bupivacaine 266 mg in 60 ml; bupivacaine hydrochloride 150 mg in 30 ml	Interscalene nerve block: ropiv 0.5%†; continuous interscalene nerve block: ropiv 0.5% (8 ml/h)	Primary outcomes listed in the results section as VAS pain levels and opioid requirements (no time point provided)				?	+	+	+	+	?	None	Not registered; primary outcome(s) inadequately defined; control group: unknown interscalene nerve block dose; postoperative cPNB for 72 h	Abildgaard[145]
Knee arthroplasty (n = 102)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg; ketorolac 30 mg (+ epinephrine) in 120 ml	Sciatic nerve block: bupivacaine hydrochloride 75 mg in 30 ml; femoral nerve block: bupivacaine hydrochloride 100 mg in 20 ml; continuous femoral nerve block: bupivacaine hydrochloride 0.2% 10 ml/h*	Median Numeric Rating Scale POD 1 06:00–12:00	4.5	3.0	0.02	?	+	+	+	?	+	Author paid consultant	Primary outcome maximum pain POD 1 from 06:00–12:00; sciatic nerve block contained clonidine 100 μg; both sciatic and femoral nerve blocks contained epinephrine; control group received bupivacaine 40 mg in 20 ml through femoral catheter on arrival to the recovery room; subjects and outcome assessors not masked to treatment group; postoperative cPNB until 06:00 on POD 2	Amundson[118]
Knee arthroplasty (n = 65)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 150 mg (+ epinephrine) in 60 ml	Femoral nerve block: bupivacaine hydrochloride 100 mg in 20 ml; continuous femoral nerve block: bupivacaine hydrochloride 0.2% 8 ml/h	VAS with maximum knee flexion on POD 1	9.0	7.9	0.02	?	+	+	+	?	+	Study funding; two authors paid consultants	Subjects and outcome assessors not masked to treatment group assignment; postoperative cPNB for 48 h	Marino[146]

(*Continued*)

Table 7. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Total shoulder arthroplasty (n = 70)	Interscalene nerve block; bupivacaine hydrochloride 100 mg in 20 ml; infiltration with liposomal bupivacaine 266 mg in 80 ml	Interscalene nerve block: bupivacaine hydrochloride 100 mg in 20 ml; continuous interscalene nerve block: bupivacaine hydrochloride 0.125% at 6 ml/h	Mean Numeric Rating Scale 0–24 h Mean Morphine mg equivalent 0–24 h	2.1 36	2.6 34	0.27 0.77	?	+	+	+	?	+	Study funding	No registration; note both groups received initial interscalene nerve block and therefore this study does not compare infiltration with liposomal bupivacaine to a single-injection block of unencapsulated local anesthetic; subjects and outcome assessors not masked to treatment group assignment; postoperative cPNB for 100 h	Sabesan[149]
Hip Surgery and Abdominal Hysterectomy															
Abdominal hysterectomy (n = 58)	Liposomal bupivacaine 266 mg in 60 ml	Bilateral transversus abdominis plane block: bupivacaine hydrochloride 200 mg in 40 ml (total)	Morphine 0–24 h VAS with coughing at 6 h	34 3.5	48 5.3	0.0497 < 0.01	-	+	+	+	+	-	Author paid consultant	Initial registration February 2014 listed "morphine consumption in the first 24 hours" as the primary outcome; December 2014 registration noted enrollment completed in September 2014 and primary outcome changed to VAS with coughing at 6 h (which matches manuscript)	Gasanova[147]

(*Continued*)

Table 7. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal Bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Risks of Bias: Conflict of Interest with Manufacturer	Comments	Reference
Hip arthroplasty (n = 105)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg (+ epinephrine) in 120 ml	Psoas nerve block: bupivacaine hydrochloride 150 mg in 30 ml (+ epinephrine); continuous psoas nerve block: bupivacaine hydrochloride 0.2% 10 ml/h*	Maximum Numeric Rating Scale POD 1 06:00–12:00	3.0	3.0	0.66	?	+	+	+	?	+	Author paid consultant	Additional control group included in table 3; liposomal bupivacaine treatment included ketorolac 30 mg; subjects and outcome assessors not masked to treatment group assignment; POD 1: bupivacaine hydrochloride cPNB changed to 0.1%; postoperative infusion until 06:00 on POD 2	Johnson[105]
Hip arthroplasty (n = 79)	Liposomal bupivacaine 266 mg in 60 ml	Fascia iliaca block: ropiv 80 mg in 20 ml *	VAS AUC 0–48 h	108	102	> 0.05	?	+	+	+	?	+	None	No registration; pain stated as primary outcome but sample size estimate based on opioid use; subjects and outcome assessors not masked to treatment group assignment; randomized, controlled trials suggest that fascia iliaca blocks do not provide effective analgesia for hip arthroplasty[152,153]	McGraw-Tatum[148]

One randomized trial compared infiltration and a peripheral nerve block, both with liposomal bupivacaine and is therefore presented in table 9.[163] Secondary outcomes are presented in table 8.

*A third control group not involving peripheral nerve blocks excluded from chart (*e.g.*, unencapsulated bupivacaine infiltration).[145] †Dosage unknown.

AUC, area under the receiver operating characteristics curve; VAS, visual analogue scale. Cochrane Risk of Bias 2 abbreviations: O, overall risk of bias; R, bias arising from the randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in selection of the reported result.

Table 8. Secondary Outcomes for Published Randomized, Controlled Clinical Trials Comparing Infiltration of Liposomal Bupivacaine and Peripheral Nerve Blocks with Unencapsulated Bupivacaine or Ropivacaine

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Single-injection Peripheral Nerve Block vs. Liposomal Bupivacaine Infiltration (Knee and Shoulder Surgery)															
Shoulder arthroplasty (n = 156)	Liposomal bupivacaine 266 mg in 40 ml	Interscalene nerve block: ropiv 150 mg in 30 ml	VAS 0 h	3.3	0.8	< 0.01	Intraoperative	16	9	< 0.01	Days	1.6	1.8	0.29	Namdari[90]
			VAS 8 h	3.2	1.4	< 0.01									
			VAS 16 h	3.8	4.3	0.35	Total	31	23						
			VAS 24 h	3.9	4.9	0.02									
Anterior cruciate ligament reconstruction (n = 82)	Liposomal bupivacaine 266 mg in 30 ml	Femoral nerve block: ropiv 200 mg in 40 ml	VAS 0–4 h	5.6	4.5	0.06	Not reported				Not reported				Okoroha[141]
			VAS 5–8 h	6.2	4.8	0.01									
			VAS 9–12 h	5.9	4.9	0.06									
			VAS 13 h	6.0	5.5	0.51									
Shoulder arthroplasty (n = 57)	Liposomal bupivacaine 266 mg in 40 ml	Interscalene nerve block: ropiv 200 mg in 40 ml	VAS 0–4 h	5.3	2.5	< 0.01	0–4 h	0.7	0.8	0.55	Days	1.5	1.5	0.97	Okoroha[142]
			VAS 5–8 h	4.9	2.5	< 0.01	5–8 h	0.7	0.8	0.16					
			VAS 9–12 h	5.0	3.7	0.12	9–12 h	0.6	0.9	0.15					
			VAS 24 h	4.5	5.4	0.18	24 h	0.5	0.7	0.45					
Knee arthroplasty (n = 80)	Liposomal bupivacaine 266 mg in 60 ml	Femoral nerve block: Ropiv 200 mg (+ epinephrine) in 50 ml	Mean Numeric Rating Scale POD 0	3.8	2.9	< 0.05	Mean POD 0	26	14	< 0.05	Days	2.4	2.7	0.03	Surdam[143]
			Mean Numeric Rating Scale POD 1	3.7	3.6	> 0.05	Mean POD 1	3.9	9.1	< 0.05					
			Mean Numeric Rating Scale POD 2	3.2	2.9	> 0.05	Mean POD 2	1.5	4.3	> 0.05					
Knee arthroplasty (n = 373)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 75 mg in 50 ml	Femoral nerve block: bupivacaine hydrochloride 50 mg in 20 ml; Infiltration bupivacaine hydrochloride 75 in 30 ml	Mean VAS 0–12 h	3.9	3.2	< 0.01	Mean 0–12 h	5.2	5.4	0.98	Days	2.8	2.7	0.51	Talmo[144]
			Mean VAS 12–24 h	4.7	4.1	< 0.01	Mean 12–24 h	8.0	8.5	0.52					
			Mean VAS 24–36 h	4.3	4.7	0.13	Mean 24–36 h	11.9	12.3	0.56					
			Mean VAS 36–48 h	4.2	4.6	0.24	Mean 36–48 h	11.2	11.8	0.67					
			Mean VAS 12 months	0.7	0.7	0.86	Mean 48–60 h	9.4	9.8	0.76					

(*Continued*)

Table 8. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Pain Scores: Measure	Pain Scores: Liposomal Bupivacaine	Pain Scores: Control	Pain Scores: *P* Value	Opioid Consumption (mg): Morphine mg Equivalents	Opioid Consumption (mg): Liposomal Bupivacaine	Opioid Consumption (mg): Control	Opioid Consumption (mg): *P* Value	Length of Stay: Measure	Length of Stay: Liposomal Bupivacaine	Length of Stay: Control	Length of Stay: *P* Value	Reference
Single-injection and/or Continuous Peripheral Nerve Block vs. Liposomal Bupivacaine Infiltration (Knee and Shoulder Surgery)															
Shoulder arthroplasty (n = 83)	Liposomal bupivacaine 266 mg in 60 ml bupivacaine hydrochloride 150 mg in 30 ml	Interscalene nerve block Ropiv 0.5% (dose?) and cPNB ropiv 0.5% (8 ml/h)	Mean VAS POD 0	5.0	3.2	< 0.05	Mean POD 0	32	6	< 0.05	Days	1.2	1.9	0.66	Abildgaard[145]
			Mean VAS POD 1	5.3	4.8	> 0.05	Mean POD 1	33	15	< 0.05					
			Mean VAS POD 2	4.1	3.5	> 0.05	Mean POD 2	65	50	> 0.05					
Knee arthroplasty (n = 102)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg; ketorolac 30 mg (+ epinephrine) in 120 ml	Sciatic nerve block: bupivacaine hydrochloride 75 mg in 30 ml; femoral nerve block: bupivacaine hydrochloride 100 mg in 20 ml; cPNB Bupivacaine hydrochloride 0.2% 10 ml/h*	Median Numeric Rating Scale (average) POD 0	2.4	0.6	< 0.01	Median POD 0	15	0	< 0.01	Days	2	2	0.77	Amundson[118]
			Median Numeric Rating Scale (average) POD 1	3.7	2.5	< 0.01	Median POD 1	45	26	< 0.01					
			Median Numeric Rating Scale (average) POD 2	3.5	3.3	0.20	Median POD 2	23	23	0.17					
Knee arthroplasty (n = 65)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 150 mg (+ epinephrine) in 60 ml	Femoral nerve block: bupivacaine hydrochloride 100 mg in 20 ml; cPNB: bupivacaine hydrochloride 0.2% 8 ml/h	Mean VAS (dynamic) 12 h	3.7	3.1	0.43		Not reported				Not reported			Marino[146]
			Mean VAS (dynamic) 24 h	4.1	5.2	0.15									
			Mean VAS (dynamic) 48 h	3.0	3.8	0.81									
			Mean VAS (dynamic) 72 h	5.5	3.1	0.87									
Shoulder arthroplasty (n = 70)	Interscalene nerve block: bupivacaine hydrochloride 100 mg in 20 ml; liposomal bupivacaine 266 mg in 80 ml	Interscalene nerve block: bupivacaine hydrochloride 100 mg in 20 ml; cPNB: bupivacaine hydrochloride 0.125% at 6 ml/h	Mean VAS 6 h	1.4	1.5	0.96	0–6 h	3	5	0.19		Not reported			Sabesan[149]
			Mean VAS 12 h	2.1	2.7	0.48	6–12 h	8	8	0.90					
			Mean VAS 18 h	2.5	2.6	0.92	12–18 h	9	12	0.54					
			Mean VAS 24 h	2.0	2.9	0.23	18–24 h	16	9	0.02					
			Mean VAS 24–48 h	2.6	3.2	0.13	0–48 h	79	53	0.23					

(*Continued*)

Table 8. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Pain Scores: Measure	Pain Scores: Liposomal Bupivacaine	Pain Scores: Control	Pain Scores: *P* Value	Opioid Consumption (mg): Morphine mg Equivalents	Opioid Consumption (mg): Liposomal Bupivacaine	Opioid Consumption (mg): Control	Opioid Consumption (mg): *P* Value	Length of Stay: Measure	Length of Stay: Liposomal Bupivacaine	Length of Stay: Control	Length of Stay: *P* Value	Reference
Hip Surgery and Abdominal Hysterectomy															
Abdominal hysterectomy (n = 58)	Liposomal bupivacaine 266 mg in 60 ml	Bilateral transversus abdominis plane block: bupivacaine hydrochloride 200 mg in 40 ml (total)	VAS with coughing 12 h	3.9	6.2	< 0.01	Hydrocodone 5 mg tablets 24–48 h	1.9	3.6	0.01	Not reported				Gasanova[147]
			VAS with coughing 24 h	4.0	6.0	< 0.01									
			VAS with coughing 48 h	3.8	5.9	< 0.01									
Hip arthroplasty (n = 105)	Liposomal bupivacaine 266 mg; bupivacaine hydrochloride 125 mg (+ epinephrine) in 120 ml	Psoas nerve block: bupivacaine hydrochloride 150 mg in 30 ml (+ epinephrine); cPNB: bupivacaine hydrochloride 0.2% 10 ml/h*	Maximum Numeric Rating Scale POD 0	4.0	4.0	0.43	POD 0 POD 1 POD 2	11 15 11	8 23 15	0.74 0.54 0.90	Days	2	2	0.77	Johnson[105]
			Maximum Numeric Rating Scale POD 1	4.0	5.0	0.47									
			Maximum Numeric Rating Scale POD 2	3.5	3.5	0.80									
Hip arthroplasty (n = 79)	Liposomal bupivacaine 266 mg in 60 ml	Fascia iliaca block: ropiv 80 mg in 20 ml *	No secondary pain score outcome measures				0–48 h	61	55	> 0.05	Hours	47	44	> 0.05	McGraw-Tatum[148]

An additional randomized trial compared infiltration with liposomal bupivacaine and bupivacaine hydrochloride for mammoplasty but was excluded due to early termination by the manufacturer.[207] Primary outcomes are presented in table 7.

*A third treatment group not involving infiltration excluded from chart (*e.g.*, continuous peripheral nerve block).

POD, postoperative day; VAS, visual analogue scale.

block group concurrently required a lower dose of supplemental opioids,[90,118,143,145] while the remainder reported little difference during this period of time.[141,142,144,146] Collectively, these eight studies provide evidence that a single-injection peripheral nerve block with unencapsulated ropivacaine or bupivacaine provides superior analgesia compared with liposomal bupivacaine infiltration for the duration of the peripheral nerve block.

However, one of the proposed benefits of using liposomal bupivacaine infiltration is the possibility of prolonging analgesia *beyond* the typical 8 to 12 h peripheral nerve block duration. Of the eight randomized, controlled trials just described,[90,118,141–146] three included an additional continuous peripheral nerve block in which unencapsulated local anesthetic was infused through a percutaneous perineural catheter to extend analgesia beyond the duration of the initial single-injection peripheral nerve block.[118,145,146] Therefore, the remaining five randomized, controlled trials describe a single-injection peripheral nerve block without a subsequent confounding perineural infusion: one reported that subjects receiving infiltrated liposomal bupivacaine did have less pain at 24 h (although not beyond),[90] with the remaining four trials finding no statistically significant differences between treatments.[141–144] Similarly, of these five trials,[90,141–144] two detected lower opioid requirements for liposomal bupivacaine subjects after block resolution: one on postoperative day 1,[143] and the other during postoperative hours 13 through 16 (although this was reversed in favor of the peripheral nerve block group during hours 49 to 56, suggesting a high probability of type I errors for these two findings due to multiple comparisons with a limited sample size).[142] Thus, these five randomized, controlled trials failed to provide evidence that liposomal bupivacaine provided any analgesic or opioid-sparing benefits beyond postoperative day 1.

Continuous Peripheral Nerve Block

Four randomized, controlled trials included a continuous peripheral nerve block for knee and shoulder surgery, allowing a comparison of liposomal bupivacaine infiltration and perineural local anesthetic infusion (tables 7 and 8).[118,145,146,149] The two involving knee arthroplasty reported lower pain scores for subjects with continuous femoral nerve blocks during the period of perineural local anesthetic infusion based on both primary and secondary outcome measures.[118,146] One of these also found concurrent lower opioid use for continuous peripheral nerve block subjects,[118] while the other detected a longer time to first use of rescue opioids for subjects who had received liposomal bupivacaine.[146]

Two additional randomized, controlled trials involved shoulder arthroplasty; neither found differences in pain scores after resolution of the single-injection peripheral nerve block.[145,149] However, both detected greater opioid sparing in favor of the continuous peripheral nerve block during this same duration. Unfortunately, neither was registered or had a well-defined primary outcome measure. In addition, one provided no information on the perineural infusion dosing in the manuscript, rendering the findings for postoperative days 1 and 2 difficult to interpret.[145] Furthermore, unlike the other continuous peripheral nerve block investigations, the second trial provided a single-injection interscalene block to *both* treatment groups.[149]

The reason for the finding of continuous peripheral nerve block analgesic superiority over infiltrated liposomal bupivacaine for femoral but not interscalene catheters is not readily apparent.[118,146,149] It may simply be due to the very low number of studies with underpowered sample sizes, or that in one shoulder study, both treatment groups received a single-injection peripheral nerve block. Regardless, this latter study is a good example of the potential benefit of local infiltration analgesia over continuous peripheral nerve blocks: two subjects experienced residual hand numbness that resolved with catheter removal, and five had an inadvertent, premature catheter dislodgement.[149] Moreover, unlike perineural infusion, tissue/joint infiltration carries little risk of inducing muscle weakness,[146] patient burden is decreased without an infusion pump and local anesthetic reservoir to carry, and provider workload is reduced without an infusion to manage.[1] Given these potential benefits of liposomal bupivacaine combined with the equivocal available comparison data, additional research is greatly needed to assist stakeholders in optimizing patients' perioperative experience.

Three studies involved hip arthroplasty or abdominal hysterectomy (tables 7 and 8).[105,148] One hip arthroplasty study compared infiltration with liposomal bupivacaine with a fascia iliaca block without a subsequent infusion,[148] while the other compared liposomal bupivacaine to single-injection and continuous psoas compartment (posterior lumbar plexus) blocks.[105] Liposomal bupivacaine infiltration was not inferior to a fascia iliaca block in the first study, but interpretation of this result is complicated by results of multiple randomized, placebo-controlled trials demonstrating that fascia iliaca blocks provide little to no analgesic benefit after hip arthroplasty.[150,151] In contrast, psoas compartment blocks/infusions do offer pain control for hip arthroplasty,[152,153] and liposomal bupivacaine infiltration was not inferior to this block, which had a high incidence of motor weakness and complications, indicating benefits from liposomal bupivacaine in this comparison.[105]

Last, one randomized, controlled trial compared liposomal bupivacaine infiltration with a bilateral transversus abdominis block with bupivacaine hydrochloride for total abdominal hysterectomy.[147] The results were statistically significant in favor of the liposomal bupivacaine infiltration for both the primary outcome of pain upon coughing 6 h after surgery and nearly every secondary pain (at rest and on coughing) and opioid endpoint from 2 to 48 postoperative hours. Unfortunately, a discrepancy between the primary

outcome provided in the registry and published manuscript results in a high risk of bias for this trial.

Summary

To summarize the evidence for the use of infiltration with liposomal bupivacaine compared with a peripheral nerve block with unencapsulated local anesthetic for knee and shoulder procedures, all of eight randomized, controlled trials found evidence that a single-injection peripheral nerve block provides superior analgesia and concurrent opioid sparing for the duration of the block based on secondary outcomes.[90,118,141–146] After block resolution, only one trial found any analgesic benefit of liposomal bupivacaine infiltration—and then only at 24 h[90]; two detected opioid sparing on postoperative day 0 or 1.[142,143] Four randomized, controlled trials are available comparing liposomal bupivacaine infiltration with a continuous peripheral nerve block, and all reported lower pain scores and/or less opioid use for subjects with continuous peripheral nerve blocks based on primary and secondary outcomes.[118,145,146,149] Therefore, there is evidence demonstrating the superiority of single-injection and/or continuous peripheral nerve blocks to liposomal bupivacaine infiltration for knee and shoulder surgery. However, the improved analgesia and opioid sparing must be balanced against the time and expertise required for administration, increased patient and provider burden, and other block-related limitations. Only a single randomized, controlled trial provides reliable data involving hip surgery, and while it does not demonstrate any superiority of liposomal bupivacaine over single-injection and continuous peripheral nerve blocks, the lack of block-related limitations will favor the liposomal bupivacaine infiltration method for many providers.[105] Finally, the one randomized, controlled trial investigating abdominal hysterectomy provides evidence that liposomal bupivacaine infiltration is superior to a bilateral transversus abdominis block with unencapsulated bupivacaine,[147] but this trial was deemed at high risk for bias due to a discrepancy between the primary outcome provided in the registry and published manuscript.[98,99]

Liposomal Bupivacaine Administered as an Epidural or Peripheral Nerve Block

Liposomal bupivacaine is approved by the Food and Drug Administration for use in two specific peripheral nerve blocks: transversus abdominis plane and interscalene (exclusively for postoperative analgesia after shoulder surgery). However, data are available for additional anatomic locations such as the epidural space, with studies performed under investigational new drug applications. We include these published randomized, controlled trials along with those investigating currently approved applications (tables 9 and 10).[29,139,154–167] The 16 disparate trials of this section are not easily categorized or compared due to their heterogenous surgical procedures, experimental treatments (*e.g.*, peripheral nerve block *vs.* epidural), and comparison groups (*e.g.*, placebo *vs.* liposomal bupivacaine).

Peripheral Nerve Block with Liposomal Bupivacaine *versus* Placebo

There are four randomized, controlled trials comparing a peripheral nerve block using liposomal bupivacaine and a placebo control.[29,139,154,160] The first involved elective coronary artery bypass grafting through a median sternotomy and sequential intercostal nerve blocks performed through the surgical incision, as well as infiltration surrounding the mediastinal drains.[154] Although the authors designated pain scores and opioid use as primary outcomes, no time point was specified, warranting "some concerns" regarding possible bias using the Cochrane tool. At none of 10 individual time points between 0 and 72 postoperative hours was liposomal bupivacaine found to be superior to placebo. However, when overall pain scores were compared using a linear mixed-effects model, the treatment group demonstrated lower scores ($P = 0.040$). Except for the 2-h time point, the treatment group did not demonstrate a significant reduction in pain medication requirements either at individual time points or overall. Similarly, there were no differences in secondary outcomes such as time to extubation, hospital or intensive care unit length of stay, time to first bowel movement, or time to return to work or daily activity. Considering the comparison group was normal saline and not active unencapsulated bupivacaine, the authors concluded, "there is currently not enough evidence to justify the clinical use of this drug for this purpose."[154]

In contrast, two other placebo-controlled trials with low risk of bias offer stronger evidence in favor of liposomal bupivacaine when administered as an ultrasound-guided femoral, or interscalene nerve block before major knee or shoulder surgery, respectively.[29,139] Subjects experienced lower pain when all scores during the first 48 to 72 postoperative hours were evaluated together using AUC. Importantly, the windowed worst-observation-carried-forward technique was employed; however, the difference between treatments remained with a *post hoc* analysis without score imputation, although the effect size was reduced by approximately 25 to 39%. With data imputation, daily pain score AUC for the 0 to 24, 24 to 48, and 48 to 72-h periods were approximately 13 to 39% (femoral) and 26 to 51% (interscalene) lower in the treatment groups, providing evidence that there is pharmacologic activity beyond 48 h. For interscalene blocks, the actual resting pain scores (not AUC) were dramatically improved for the active treatment—approximately 30 to 60% lower—for all three time periods, as was the opioid consumption (reduced by 66 to 86%). In contrast, benefits for femoral blocks were far more modest, with resting pain scores and opioid consumption improved to a clinical and statistically significant degree only through 24 h. One important caveat is that neither

Table 9. Published Randomized, Controlled Clinical Trials Involving Liposomal Bupivacaine as Part of a Peripheral Nerve Block or Epidural Injection

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Placebo-controlled Studies															
Knee arthroplasty (n = 164)	Femoral nerve block liposomal bupivacaine 266 mg in 20 ml	Placebo femoral nerve block normal saline 20 ml	Numeric Rating Scale at rest AUC 0–72 h	419	516	< 0.01	+	+	+	+	+	+	Company provided funding; participated in conception and design; collection, analysis, and interpretation of data; and manuscript review; four authors paid consultants and 1 stockholder	Phase III multicenter trial: dose-ranging pilot study ("Part 1") data not included in this table; primary pain outcome calculated with windowed worst-observation-carried-forward and last-observation-carried-forward but provided results with and without the imputation along with daily pain scores; liposomal bupivacaine not Food and Drug Administration–approved for use in a femoral nerve block, but investigational drug application filed	Hadzic[139]
Hysterectomy (n = 62)	Transversus abdominis plane block: liposomal bupivacaine 133 mg; bupivacaine hydrochloride 25 mg 30 ml bilaterally; port sites infiltration normal saline	Placebo transversus abdominis plane block: saline 30 ml bilaterally; port site infiltration: bupivacaine hydrochloride 25 mg in 10 ml per site	Total morphine mg equivalent 0–72 h	21	25	0.03	+	+	+	+	+	+	First and third authors paid consultants	Experimental treatment: bilateral transversus abdominis plane block with liposomal bupivacaine and bupivacaine hydrochloride; placebo at port sites; control treatment: placebo transversus abdominis plane block; bupivacaine hydrochloride only at port sites; therefore, two different independent variables varied and unknown which or both responsible for observed outcome differences; no median/mean Numeric Rating Scale provided	Hutchins (2019)[160]

(*Continued*)

Table 9. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Liposomal bupivacaine	Control	*P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Coronary bypass sternotomy (n = 79)	Intercostal nerve block *(via* surgical incision): liposomal bupivacaine 266 mg in 50 ml	Placebo intercostal nerve block *(via* surgical incision): normal saline 50 ml	Total morphine mg equivalent 0–72 h Median Numeric Rating Scale 0–72 h	Not reported		0.18 0.04	?	+	+	+	+	?	No statement on funding or conflicts of interest, but none listed in registry entry or found on the Open Payments website	Dual primary outcome measures but no time point(s) designated; authors concluded that liposomal bupivacaine "may provide marginal improvement in overall pain scores; however, this does not seem to translate into significant improvements in objective clinical measures. Therefore, we believe that there is currently not enough evidence to justify the clinical use of this drug for this purpose"[154]	Lee[154]
Shoulder arthroplasty and rotator cuff repair (n = 140)	Interscalene nerve block: liposomal bupivacaine 133 in 20 ml	Placebo interscalene nerve block: normal saline 20 ml	VAS AUC 0–48 h	254	136	< 0.01	+	+	+	+	+	+	Study funding; at least four authors paid consultants; author company employee	Phase III multicenter trial; liposomal bupivacaine 266 mg group discontinued (n = 15) and data excluded from analysis; primary pain outcome calculated with windowed worst-observation-carried-forward and last-observation-carried-forward but provided results with and without the imputation along with daily pain scores	Patel[29]
Active-controlled: Transversus Abdominis Plane															
Colorectal surgery (n = 200)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 20 ml bilaterally	Intrathecal hydromorphone 100 μg	VAS AUC 0–48 h Total morphine mg equivalent 0–48 h	3.0 48	2.4 33	< 0.01 0.10	?	+	+	+	?	+	None	Coprimary outcomes pain scores (AUC) and opioid use 0–48 h, but sample size based on pain scores alone; subjects not masked to treatment; unclear if outcome assessors masked	Colibaseanu[155]

(*Continued*)

Table 9. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Colorectal surgery (n = 179)	Transversus abdominis plane block: liposomal bupivacaine 133 mg (bupivacaine hydrochloride†; n = 15) in 20 ml bilaterally	Epidural bupivacaine hydrochloride 0.0625% fentanyl† 6–8 ml/h	Unclear primary outcome measure(s)				-	+	+	+	?	-	None	Primary outcome different in registry and article; results not provided for either; unexplained change in the intervention for transversus abdominis plane block group: 15 subjects received bupivacaine hydrochloride; neither outcome assessors nor subjects masked to treatment group	Felling[156]
Breast reconstruction (n = 44)	Transversus abdominis plane block (*via* surgical incision): liposomal bupivacaine 266 mg in 50 ml	Transversus abdominis plane block (*via* surgical incision): bupivacaine hydrochloride 75 mg in 45 ml	Total morphine mg equivalent 0–72 h	283	300	0.98	?	+	+	+	?	?	None	Not registered; all subjects received preoperative T2–T4 paravertebral blocks (bupivacaine hydrochloride 0.5% 15 ml); stopped due to futility (but the stopping rules were not prospectively defined); unclear which individuals were masked to treatment (if any)	Ha[157]
Hysterectomy (n = 58)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 30 ml bilaterally	Transversus abdominis plane block: bupivacaine hydrochloride 75 mg in 30 ml (+ epinephrine) bilaterally	Total morphine mg equivalent 0–72 h	25	52	< 0.01	-	+	+	+	+	-	First author paid consultant	First registered 1 month after enrollment completion; registry primary outcome first listed as "post operative pain scores" 0–72 h; subsequently changed to morphine mg equivalents 0–72 h (matches article); no median/mean Numeric Rating Scale provided	Hutchins (2015)[158]
Donor nephrectomy (n = 59)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 30 ml bilaterally	Transversus abdominis plane block: bupivacaine hydrochloride 75 mg in 30 ml (+ epinephrine) bilaterally	Median Maximum Numeric Rating Scale 48–72 h	3	5	0.02	-	+	+	+	+	-	First author paid consultant	First registered 4 months after enrollment completion; no primary outcome designated in article; registry: primary outcome first listed as "postoperative pain control" 0–72 h; subsequently changed to maximum Numeric Rating Scale 48–72 h; no median/mean Numeric Rating Scale provided	Hutchins (2016)[159]

(*Continued*)

Table 9. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Risks of Bias: Conflict of Interest with Manufacturer	Comments	Reference
Cesarean delivery (n = 186)	Transversus abdominis plane block: liposomal bupivacaine 133 mg; bupivacaine hydrochloride 25 mg in 30 ml bilaterally	Transversus abdominis plane block: bupivacaine hydrochloride 25 mg in 30 ml bilaterally	Total morphine mg equivalent 0–72 h	16	32	0.01	-	+	+	-	+	+	Study funding; two authors paid consultants; two authors company employees who "may own stock or stock options in the company"	Protocol revised during enrollment with first two cohorts excluded completely; a total of 28% of randomized subjects excluded from primary outcome measurement; among these subjects, those receiving liposomal bupivacaine required more opioid 0–72 h than the control group: 52 mg *vs* 11 mg (*P* value not reported); lowest concentration of bupivacaine hydrochloride relative to all other published single-injection transversus abdominis plane block randomized controlled trials (<0.09%) and among the lowest—if not the lowest—bupivacaine hydrochloride doses relative to all other published single-injection transversus abdominis plane block randomized controlled trials[168,169]	Nedeljkovic[161]
Colorectal surgery (n = 83)	Transversus abdominis plane block liposomal bupivacaine 133 mg in 40 ml bilaterally	Epidural bupivacaine hydrochloride 0.0625% fentanyl 2 μg/ml at unknown rate for 2 days	Mean hospital length of stay (h)	75	86	0.045	?	+	+	+	?	+	No information provided	Not registered; control group: subjects undergoing laparoscopy had 1% lidocaine and 0.25% bupivacaine hydrochloride (+ epinephrine); unknown volume at each trocar site; neither outcomes assessors nor subjects masked to treatment group assignment; no pain scores or opioid use reported	Torgeson[162]

(*Continued*)

Table 9. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Active-controlled: Miscellaneous															
Knee arthroplasty (n = 70)	Adductor canal block: liposomal bupivacaine 266 mg in 20 ml	Joint infiltration: liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 40 ml	Primary outcome described as "mean pain scores for the first 3 days," but no results combining POD 0–3 provided; therefore, primary outcome unclear				?	+	+	+	+	?	None	Not registered; liposomal bupivacaine not Food and Drug Administration–approved for use in an adductor canal block but no investigational new drug application filed	Meftah[163]
Hip arthroscopy (n = 70)	Fascia iliaca block: liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 40 ml	Fascia iliaca block: bupivacaine hydrochloride 100 mg in 40 ml	Defense Veterans Pain Rating Scale	Each of five time points were included in the primary outcome: see table 10 for specific days		> 0.05	+	+	+	+	+	+	None	Liposomal bupivacaine not Food and Drug Administration–approved for use in a fascia iliaca block but no investigational new drug application filed	Purcell[164]
Upper extremity surgery (n = 37)	Median, ulnar, radial nerve blocks: liposomal bupivacaine 65 mg in 5 ml to each nerve; supraclavicular block: mepivacaine 450 mg in 30 ml	Supraclavicular nerve block: bupivacaine hydrochloride 150 mg in 30 ml	Authors "considered the results of the EuroQol 5D–5L instrument the primary outcome" but this includes 18 separate outcomes (all >0.05)				-	+	+	+	+	-	Study funding	Primary outcome per registry: onset of sensory block; but per article: EuroQol POD 0, 1, 2, 3; liposomal bupivacaine not Food and Drug Administration–approved for use in a fascia iliaca block but no investigational new drug application filed	Soberon[165]

(*Continued*)

Table 9. (Continued)

Setting	Treatments: Experimental	Treatments: Control	Primary Outcome: Measure	Primary Outcome: Liposomal bupivacaine	Primary Outcome: Control	Primary Outcome: *P* Value	Risks of Bias: Cochrane Risk of Bias 2: O	R	D	Mi	M	S	Conflict of Interest with Manufacturer	Comments	Reference
Shoulder surgery (n = 50)	Interscalene block liposomal bupivacaine 133 mg bupivacaine hydrochloride 12.5 mg in 15 ml	Interscalene block bupivacaine hydrochloride 37.5 mg in 15 ml	Worst Numeric Rating Scale POD 2	3.6	5.5	> 0.05	-	+	+	+	+	-	Study funding; 1 author paid consultant	Discrepancy in original and final primary outcome measures designated in the registry[175,176]; primary outcome described in article as "worst pain during in the first postoperative week," but the sample size analysis based on worst Numeric Rating Scale POD 2; no median/mean Numeric Rating Scale provided; liposomal bupivacaine not Food and Drug Administration–approved for use in the epidural space, but investigational drug application filed	Vandepitte[166]
			Worst Numeric Rating Scale POD 1, 2, 3, 4, 7 using a generalized estimating equation	3.6	5.3	< 0.01									
Healthy volunteers (n = 26)	Epidural liposomal bupivacaine 89 mg, 155 mg, or 266 mg in 20 ml	Lumbar epidural (L3–4) bupivacaine hydrochloride 50 mg (in unknown volume)	Exploratory study without a primary outcome				+	+	+	+	+	+	Company provided funding; participated in design, analysis, and manuscript preparation; first author paid consultant; one author company employee	Not registered (before enactment of the International Committee of Medical Journal Editors Guidelines); phase I–II exploratory study using a convenience sample; liposomal bupivacaine not Food and Drug Administration–approved for use in the epidural space, but investigational drug application filed	Viscusi[167]

Secondary outcomes are presented in table 10.

*A third control group not involving peripheral nerve blocks excluded from chart (*e.g.*, unencapsulated bupivacaine infiltration).[145] †Dosage unknown.

AUC, area under the receiver operating characteristics curve; VAS, visual analogue scale. Cochrane Risk of Bias 2 abbreviations: O, overall risk of bias; R, bias arising from the randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in selection of the reported result.

Table 10. Secondary Outcomes for Published Randomized, Controlled Clinical Trials Involving Liposomal Bupivacaine as Part of a Peripheral Nerve Block or Epidural Injection

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Placebo-controlled Studies															
Knee arthroplasty (n = 164)	Femoral nerve block: liposomal bupivacaine 266 mg in 20 ml	Femoral nerve block: normal saline 20 ml	Numeric Rating Scale at rest 24 h	3.5	5.0	< 0.01	0–24 h	46	60	< 0.01		Not reported			Hadzic[139]
			Numeric Rating Scale at rest 48 h	2.7	3.1	> 0.05	24–48 h	16	23	> 0.05					
			Numeric Rating Scale at rest 72 h	2.2	1.9	> 0.05	48–72 h	7	11	> 0.05					
Coronary bypass sternotomy (n = 79)	Intercostal nerve block (*via* surgical incision): liposomal bupivacaine 266 mg in 50 ml	Intercostal nerve block (*via* surgical incision): normal saline 50 ml	Numeric Rating Scale 24 h	2	4	> 0.05	24 h	12	18	> 0.05	Days	5	5	0.14	Lee[154]
			Numeric Rating Scale 48 h	1.5	2		48 h	4	3						
			Numeric Rating Scale 72 h	1	0		72 h	3	3						
Shoulder arthroplasty and rotator cuff repair (n = 140)	Interscalene nerve block: liposomal bupivacaine 133 or 266 mg in 20 ml	Interscalene nerve block normal saline 20 ml	VAS 24 h	2.5	5.5	< 0.01	0–24 h	5	34	< 0.01	Hours until discharge readiness (not actual discharge)	11	22	< 0.01	Patel[29]
			VAS 48 h	3.0	4.2	0.03	24–48 h	4	14						
			VAS 72 h	2.5	4.0	< 0.01	48–72 h	4	12						
Active-controlled: Transversus Abdominus Plane															
Colorectal surgery (n = 200)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 20 ml bilaterally	Intrathecal hydromorphone 100 μg	Mean VAS 8 h	3.0	1.4	< 0.01	POD 0	25	15	< 0.01	Days	3	3	0.09	Colibaseanu[155]
			Mean VAS 16 h	3.2	2.2	0.02	POD 1	8	7.5	0.20					
			Mean VAS POD 1	2.8	2.8	0.86	POD 2	0	7.5	0.25					
			Mean VAS POD 2	2.5	2.8	0.41									
Colorectal surgery (n = 179)	Transversus abdominis plane block: liposomal bupivacaine 133 mg (bupivacaine hydrochloride†; n = 15) in 20 ml bilaterally	Epidural bupivacaine hydrochloride 0.0625% fentanyl† 6–8 ml/h	Numeric Rating Scale POD 0–3	2.3	2.1	0.387	POD 0	55	28	< 0.01		Not reported			Felling[156]
							POD 1	13	1	< 0.01					
							POD 2	3	2	0.71					
							POD 3	0	0	0.85					

(*Continued*)

Table 10. (Continued)

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Breast reconstruction (n = 44)	Transversus abdominis plane block (*via* surgical incision): liposomal bupivacaine 266 mg in 50 ml	Transversus abdominis plane block (*via* surgical incision): bupivacaine hydrochloride 75 mg in 45 ml	Median Numeric Rating Scale 12 h	0	2	0.39	Intraoperative	110	100	0.76	Days	2.9	3.6	0.20	Ha[157]
							Recovery	10	0	0.38					
			Median Numeric Rating Scale 24 h	3	2		On floor	139	165	0.69					
			Median Numeric Rating Scale 48 h	2	2										
			Median Numeric Rating Scale 72 h	0.5	2										
Hysterectomy (n = 58)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 30 ml bilaterally	Transversus abdominis plane block bupivacaine hydrochloride 75 mg in 30 ml (+ epinephrine) bilaterally	Median Maximum Numeric Rating Scale 0–24 h	4.5	7.0	< 0.01	0–24 h	13	25	0.02	Hours	11	17	0.055	Hutchins (2015)[158]
			Median Maximum Numeric Rating Scale 24–48 h	4.0	5.0	0.044	24–48 h	3	8	0.02					
			Median Maximum Numeric Rating Scale 48–72 h	3.0	5.0	0.047	48–72 h	2	5	0.30					
Donor nephrectomy (n = 59)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 30 ml bilaterally	Transversus abdominis plane block: bupivacaine hydrochloride 75 mg in 30 ml (+ epinephrine) bilaterally	Median Maximum Numeric Rating Scale 0–24 h	6	6	> 0.05	Fentanyl equivalents 0–24 h	≈200	≈220	> 0.05	Hours	68	78	0.02	Hutchins (2016)[159]
			Median Maximum Numeric Rating Scale 24–48 h	5	6	< 0.01	Fentanyl equivalents 24–48 h	200	230	> 0.05					
							Fentanyl equivalents 48–72 h	105	182	0.03					
Hysterectomy (n = 62)	Transversus abdominis plane block: liposomal bupivacaine 133 mg; bupivacaine hydrochloride 25 mg 30 ml bilaterally; port sites infiltration normal saline	Port site infiltration; bupivacaine hydrochloride 25 mg in 10 ml per site; placebo transversus abdominis plane block saline 30 ml bilaterally	Median Maximum Numeric Rating Scale 0–24 h	3.0	5.0	0.02	Median 0–24 h	8	23	0.14	Hours (in recovery room)	3.3	3.1	0.98	Hutchins (2019)[160]
			Median Maximum Numeric Rating Scale 24–48 h	3.0	4.0	0.22	Median 24–48 h	0	8	0.27					
			Median Maximum Numeric Rating Scale 48–72 h	2.0	3.0	< 0.01	Median 48–72 h	0	5	0.24					

(*Continued*)

Table 10. (Continued)

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Cesarean delivery (n = 186)	Transversus abdominis plane block: liposomal bupivacaine 133 mg; bupivacaine hydrochloride 25 mg in 30 ml bilaterally	Transversus abdominis plane block: bupivacaine hydrochloride 25 mg in 30 ml bilaterally	VAS AUC 0–72	148	179	> 0.05 (LSM *P* = 0.002, but 95% CI includes 0)	0–24 h 0–48 h	2 9	6 21	> 0.05 0.01	Not reported				Nedeljkovic[161]
Colorectal surgery (n = 83)	Transversus abdominis plane block: liposomal bupivacaine 133 mg in 40 ml bilaterally	Epidural bupivacaine hydrochloride 0.0625% fentanyl 2 μg/ml at unknown rate		Not reported				Not reported			Primary outcome measure presented in table 9				Torgeson[162]
Active-controlled: Miscellaneous															
Knee arthroplasty (n = 70)	Adductor canal block: liposomal bupivacaine 266 mg in 20 ml	Joint infiltration liposomal bupivacaine 266 mg: bupivacaine hydrochloride 100 mg in 40 ml	Mean VAS 4–12 h	3.9	3.1	0.13	Mean 4–12 h	24	16	0.22	Days	2.3	1.6	0.14	Meftah[163]
			Mean VAS POD 1	5.3	4.3	0.09	Mean POD 1	47	45	0.64					
			Mean VAS POD 2	3.3	2.9	0.42	Mean POD 2	39	37	0.52					
			Mean VAS POD3	4.8	1.8	0.04	Mean POD 3	37	36	0.75					
Hip arthroscopy (n = 70)	Fascia iliaca block: liposomal bupivacaine 266 mg; bupivacaine hydrochloride 100 mg in 40 ml	Fascia iliaca block: bupivacaine hydrochloride 100 mg in 40 ml	Defense and Veterans Pain Rating Score				Oxycodone (5-mg tablets) POD 1	4	3	0.61		Not reported			Purcell[164]
			Recovery room	4	4	0.68	Oxycodone (5-mg tablets) POD 2	3	3	0.53					
			POD 1	3	3	0.63									
			POD 2	3	3	0.90	Oxycodone (5-mg tablets) POD 3	2	2	0.25					
			POD 3	3	4	0.66	Oxycodone (5-mg tablets) POD 14	17	20	0.69					
			POD 14	2	2	0.97									

(*Continued*)

Table 10. (Continued)

	Treatments		Pain Scores				Opioid Consumption (mg)				Length of Stay				
Setting	Experimental	Control	Measure	Liposomal Bupivacaine	Control	*P* Value	Morphine mg Equivalents	Liposomal Bupivacaine	Control	*P* Value	Measure	Liposomal Bupivacaine	Control	*P* Value	Reference
Upper extremity surgery (n = 37)	Median, ulnar, radial nerve blocks: liposomal bupivacaine 65 mg in 5 ml to each nerve; supraclavicular block: mepivacaine 450 mg in 30 ml	Supraclavicular nerve block: bupivacaine hydrochloride 150 mg in 30 ml	Mean VAS 24 h	6.6	7.1	> 0.05	Subjects (n) reporting pain in the postanesthesia care unit	3	0	0.04	Postanesthesia care unit stay (min)	81	96	> 0.05	Soberon[165]
			Mean VAS 48 h	7.4	7.6										
			Mean VAS 72 h	7.5	7.2										
Shoulder surgery (n = 50)	Interscalene block: liposomal bupivacaine 133 mg; bupivacaine hydrochloride 12.5 mg in 15 ml	Interscalene block: bupivacaine hydrochloride 37.5 mg in 15 ml	Worst Numeric Rating Scale POD 1	2.3	4.0	> 0.05	Mean tramadol (mEq) POD 1	0.6	0.4	> 0.05	All subjects discharged POD 1				Vandepitte[166]
			Worst Numeric Rating Scale POD 2	3.6	5.5		Mean tramadol (mEq) POD 2	2.6	1.6						
			Worst Numeric Rating Scale POD 3	3.8	5.8		Mean tramadol (mEq) POD 3	2.3	3.2						
			Worst Numeric Rating Scale POD 4	4.4	5.3		Mean tramadol (mEq) POD 4	2.5	2.7						
			Worst Numeric Rating Scale POD 7	4.1	5.2		Mean tramadol (mEq) POD 7	2.4	2.6						
Healthy volunteers (n = 26)	Epidural liposomal bupivacaine 89 mg, 155 mg, or 266 mg in 20 ml	Lumbar epidural (L3–4) bupivacaine hydrochloride 50 mg in unknown volume	Median time to recovery of sensitivity to pinprick (h)	36	12	Not reported	Not applicable: healthy volunteers				Not applicable: healthy volunteers				Viscusi[167]

Primary outcomes are presented in table 9.

*A third control group not involving peripheral nerve blocks excluded from chart (*e.g.*, unencapsulated bupivacaine infiltration).[145] †Dosage unknown.

AUC, area under the receiver operating characteristics curve; POD, postoperative day; VAS, visual analogue scale.

investigation allowed unencapsulated local anesthetic infiltration or perioperative nonsteroidal anti-inflammatory drug administration, both of which can be important components of multimodal analgesia frequently provided for major joint surgery. Regardless, these studies suggest that single-injection femoral and interscalene nerve blocks with liposomal bupivacaine have pharmacologic activity greater than 48 h when compared to placebo—far longer than would be expected for unencapsulated bupivacaine.

Somewhat less informative for liposomal bupivacaine effectiveness is the fourth placebo-controlled study involving laparoscopic hysterectomy comparing bilateral transversus abdominis plane with a combination of liposomal bupivacaine and bupivacaine hydrochloride to a placebo (but with port site infiltration of unencapsulated bupivacaine).[160] While the difference between treatments was statistically significant for the primary outcome of 72-h cumulative opioid consumption, the 1.5 mg per day difference suggests clinical irrelevance. However, the secondary analgesic outcomes are both statistically and clinically significant for most of this same time period. Unfortunately, since two independent variables were varied—both the type of local anesthetic and the location of administration (transversus abdominis plane *vs.* ports)—it remains unknown if the observed outcome differences are related to the use of liposomal bupivacaine.

Transversus Abdominis Plane Block with Liposomal Bupivacaine *versus* an Active Control

Of the 12 randomized, controlled trials comparing a peripheral or epidural nerve block using liposomal bupivacaine and an active control, seven involve the transversus abdominis plane block (tables 9 and 10).[155–159,161,162] When the control group consisted of a transversus abdominis plane with unencapsulated bupivacaine, the results were mixed: one study involving abdominally based autologous breast reconstruction detected no statistically significant differences between the two treatments,[157] while three randomized, controlled trials involving hysterectomy and donor nephrectomy reported analgesic and opioid-sparing benefits of liposomal bupivacaine over unencapsulated bupivacaine.[158,159,161] Unfortunately, these last three trials were at high risk of bias: two due to registration occurring after enrollment completion and a change in primary outcome after the initial registration,[158,159] and the third resulting from protocol revisions during the enrollment period with 28% of randomized subjects excluded from the primary analysis.[161] Notably, of the 50 excluded subjects, total opioid consumption through 72 h was five times *higher* with liposomal bupivacaine added to unencapsulated bupivacaine (52.1 mg) than with bupivacaine hydrochloride alone (10.5 mg). This third study also used the lowest concentration of bupivacaine hydrochloride (less than 0.09%) and among the lowest—if not the lowest—bupivacaine hydrochloride dose for the control group relative to all other published single-injection transversus abdominis plane randomized, controlled trials.[168,169]

Two of the remaining three trials involving a liposomal bupivacaine transversus abdominis plane block included an epidural infusion as the control group.[156,162] The first trial involving colorectal surgery, listed different primary outcome measures in the registry and manuscript, lacked a power analysis for sample size, and provided a statistical plan lacking detail.[156] These factors render interpreting the study results problematic. Pain scores were collected at 11 time points during 4 days, and the registry lists three primary outcome measures as these scores on each of the first 3 postoperative days; however, only a single undefined pain score comparison is reported for the published article with the difference between treatments failing to reach statistical significance. The investigators concluded that the two treatments provide "equal" analgesia even though superiority and not equivalence statistical tests were applied ("absence of proof is not proof of absence").[170] In contrast, supplemental opioid requirements for the liposomal bupivacaine transversus abdominis plane group were twice that of the epidural subjects on postoperative days 0, 1, and 0 through 3 ($P < 0.001$), suggesting improved analgesia with the neuraxial technique.

The second randomized, controlled trial, also involving colorectal surgery, found that subjects with a liposomal bupivacaine transversus abdominis plane had a shorter hospital stay of 0.5 days (primary outcome) compared with those who received the epidural infusion for colorectal procedures.[162] However, interpretation is difficult as the only three secondary outcomes presented—time to flatus, nausea, and urinary retention—were all negative, and no pain scores or opioid consumption were recorded. Therefore, the reason for the shorter hospitalization remains unclear. These two trials fail to bring much clarity to the issue. An unpublished, multicenter (n = 493), prospectively registered randomized, controlled trial (NCT02996227) found that after abdominal surgery, subjects with a liposomal bupivacaine transversus abdominis plane experienced noninferior analgesia compared with the epidural group, but required more opioids to achieve this level of pain control (principal investigator, Alparslan Turan, M.D.; presentation, American Society of Anesthesiologists 2019 by Barak Cohen, M.D.). Full publication of these results will add meaningfully to this literature.

The final randomized, controlled trial comparing liposomal bupivacaine transversus abdominis plane to intrathecal hydromorphone for colorectal procedures demonstrated lower pain scores and opioid requirements for control subjects with intrathecal hydromorphone during the first 48 postoperative hours.[155] However, when discrete time periods were compared, differences were detected solely during the anticipated duration of the intrathecal opioid of approximately 12 to 16 h.[171] Secondary outcomes such as the duration of hospital stay and postoperative ileus were negative with the exception of cost, which was consistently

higher in the liposomal bupivacaine transversus abdominis plane group.

Non–Transversus Abdominis Plane Peripheral Nerve Blocks with Liposomal Bupivacaine *versus* an Active Control

Five remaining randomized, controlled trials involve different surgical procedures, interventions, control groups, and primary outcomes (tables 9 and 10).[163–167] Three of these do not provide actionable information regarding liposomal bupivacaine when used in a peripheral nerve block, all for different reasons.[163–165] The first compared liposomal bupivacaine as part of an adductor canal nerve block and liposomal bupivacaine infiltrated directly into the joint for knee arthroplasty, revealing essentially no differences in analgesia or opioid consumption.[163] Since both treatment groups included liposomal bupivacaine, the results do not provide information on liposomal bupivacaine *versus* unencapsulated local anesthetic. A second trial found no analgesic or opioid requirement differences between liposomal bupivacaine and unencapsulated bupivacaine when used in a fascia iliaca block for hip arthroplasty.[164] Unfortunately, as noted previously, placebo-controlled clinical trials demonstrate that this peripheral nerve block provides poor, if any, analgesia for hip arthroplasty,[150,151] and consequently, the results of this study are not particularly enlightening.[172] A third investigation randomized subjects having upper extremity orthopedic surgery to either three forearm nerve blocks (median, ulnar, radial) followed by a supraclavicular block with mepivacaine, or a single supraclavicular block with unencapsulated bupivacaine.[165] Interpreting the results is difficult since the investigators varied two independent variables (block location and local anesthetic type), so it remains unknown to what to attribute the few differences detected between treatments.

A fourth investigation involved subjects having major shoulder surgery who all received an interscalene block with bupivacaine hydrochloride and were then randomly administered either liposomal bupivacaine or additional bupivacaine hydrochloride.[166] Interpreting the results is difficult due to an unclear primary outcome measure. Within the text of the published article, the primary outcome is specified as the worst pain queried on postoperative day 2 (for the previous 24 h) with a matching sample size estimate—and the difference between treatments was not statistically significant for this endpoint. In contrast, the article abstract states the primary outcome as the worst pain during the entire first postoperative week.[173,174] Unfortunately, the prospective registration does not help resolve this issue due to a registry–publication discrepancy.[175,176] Average/median pain scores and opioid consumption were not presented, and the two groups did not differ to a statistically significant degree in daily worst pain scores, overall benefit of analgesic scores, and cumulative supplemental analgesic consumption. However, chi-square tests of worst pain scores and overall benefit of analgesic scores across all time points (postoperative days 1 to 7) based on generalized estimating equations were statistically significant. Unfortunately, no hierarchical or alpha-spending testing strategy was prespecified to control type I error across outcomes, time points, and the generalized estimating equations chi-square tests. A Bonferroni correction was used to adjust *P* values for the five time points within an outcome, but the chi-square test was not corrected. The *P* values for generalized estimating equations *t* tests applied at each time point were not reported. Combined, all of these issues decrease confidence in the conclusion that adding liposomal bupivacaine to unencapsulated bupivacaine single-injection interscalene nerve blocks resulted in clinical benefits. Of additional concern, a retrospective study of 352 patients who received liposomal bupivacaine as part of an interscalene nerve block for ambulatory shoulder surgery found that 12% returned to the emergency department due to dyspnea.[177]

Epidural Administration

In preclinical studies, liposomal bupivacaine exhibited no toxicity when administered in the epidural space of both rats and dogs.[178] The only published clinical trial involved 26 volunteers given a single 20-ml injection into the lumbar epidural space consisting of liposomal bupivacaine (89, 155, or 266 mg) or bupivacaine hydrochloride (50 mg).[167] Due to the relatively small number of subjects in each treatment group of this phase I study, no statistics were applied to the collected data. Nevertheless, the results of this pilot study strongly suggest a dramatic increase in analgesia duration: median time until recovery of pinprick sensation was 11 h for unencapsulated bupivacaine, compared with 35 h for liposomal bupivacaine (all doses combined). In contrast, 100% of those receiving bupivacaine hydrochloride had some degree of motor block compared with only 57% for the liposomal bupivacaine group. This left 67% of those in the unencapsulated bupivacaine group unable to ambulate after 4 h *versus* only 39% for those who had received liposomal bupivacaine. There were no serious adverse events. *It is emphasized that Exparel is not currently approved for use in the epidural space, and although promising, must be considered experimental at this time.*

Summary

A succinct summary of the evidence for the use of liposomal bupivacaine within an epidural or peripheral nerve block is challenging due to the heterogeneity of the 16 published randomized, controlled trials (tables 9 and 10).[29,139,154–167] The four placebo-controlled trials provide evidence of pharmacologic effects for more than 48 h, although clinical benefit was often limited to 24 h.[139,154] Based on seven randomized, controlled trials—four with a high risk of bias and the remaining three with "some concerns" regarding bias—the evidence is mixed regarding the benefits of liposomal

bupivacaine over unencapsulated bupivacaine in transversus abdominis plane blocks, possibly due to various surgical applications or administration protocols.[155–159,161,162] While the limited data suggest that epidural and intrathecal opioids provide superior analgesia and/or are opioid-sparing compared with liposomal bupivacaine transversus abdominis planes, they may also prolong hospitalization, induce hypotension, and increase overall costs.[155,156,162] Although four randomized, active-controlled trials involve using liposomal bupivacaine as part of a peripheral nerve other than a transversus abdominis plane block, three provide minimal useful data for various reasons,[163–165] and interpreting the fourth is problematic.[166] Thus, there are currently insufficient data to conclusively support or refute the use of liposomal bupivacaine administered as a peripheral nerve block. Last, a single injection of liposomal bupivacaine into the epidural space more than tripled the duration of sensory effects to skin testing while greatly decreasing any motor block in a small cohort of healthy volunteers.[167]

Randomized *versus* Retrospective Data Discrepancies

Sustained released local anesthetic offers the possibility of prolonging postoperative analgesia beyond the normal duration of unencapsulated bupivacaine. Since liposomal bupivacaine may be detected within the serum more than twice as long as bupivacaine hydrochloride,[31] the findings suggesting liposomal bupivacaine benefits reported in early cohort and case-control studies appeared reasonable—even obvious.[55–78] However, the strength of evidence for clinical effectiveness provided by randomized, controlled trials far surpasses that of nonexperimental study designs, and there are now more than 76 published experimental investigations. As detailed in this review, the preponderance of high-quality evidence fails to support the retrospective data: when liposomal bupivacaine and unencapsulated local anesthetic were infiltrated directly into a surgical site, only four of 36 randomized, controlled trials (11%) were positive for their primary outcome to a clinically relevant degree. Indeed, recent meta-analyses that included exclusively randomized studies universally concur[3–7]—in contrast to meta-analyses that included retrospective investigations and universally reported liposomal bupivacaine superiority.[179–185] The overwhelming majority of randomized, controlled trials failed to demonstrate liposomal bupivacaine superiority even though the dose of liposomal bupivacaine was almost always maximized, while that of the comparator was rarely optimized. Even when compared to a placebo, infiltration with liposomal bupivacaine improved effects in only a minority of randomized, controlled trials (42%).

We can only speculate on possible reasons for these unexpected findings where most randomized, controlled trials did not support the positive effects of liposomal bupivacaine suggested in retrospective studies. It may be that while bupivacaine hydrochloride is slowly released from the liposomes and detectable in serum over a prolonged duration, the concentration of local anesthetic at the target nerves is often subtherapeutic. Evidence for this may be found in the lower potency of liposomal bupivacaine: unlike bupivacaine hydrochloride, encapsulated bupivacaine will not provide a surgical block,[186] and for this reason, the manufacturer recommends "the ability to admix long-acting liposomal bupivacaine with immediate-release bupivacaine [which] can help ensure rapid onset of pain relief that spans both the acute and later postsurgical periods."[135] Just as clinical effects are limited to less than 18 h after administration of unencapsulated bupivacaine—even though this medication may be detected in the serum for two to three times this duration—so too might the clinical effects of liposomal bupivacaine be limited to far less time than serum concentration might suggest.[139]

Risk of Bias

Of the 76 clinical trials included in this review, the Cochrane risk-of-bias tool identified 19 (25%) with a high overall risk of bias.[98,99] It is notable that of the 19 deemed at high risk for bias, 84% (16) reported statistically significant differences for their primary outcome measure(s) compared with only 14% (4) of the 28 trials with a low risk of bias (fig. 2). Multiple factors accounted for trials with a high risk of bias. The most common was a lack of a prospectively designated or inadequately defined primary outcome measure, which increases the risk of selective reporting. This was one of the primary reasons for requiring prospective registration,[187] which 29 (38%) lacked within this review. Few of the 76 randomized, controlled trials had a prospectively determined plan for statistical analysis, which can greatly increase the risk of bias due to so-called "data torturing."[188] Even with a prospective analytic plan, deviations can dramatically affect the results, as evidenced by one trial involving infiltration for knee arthroplasty reporting superiority of liposomal bupivacaine, when no statistically significant difference would exist had the original published statistical plan been followed.[130,140] Similarly, selectively removing randomized subjects can alter study results, avoidance of which is the purpose of intention-to-treat analysis ("once randomized, always randomized"). For example, one randomized, controlled trial reported superiority of liposomal bupivacaine added to unencapsulated bupivacaine over bupivacaine hydrochloride alone within postcesarean delivery transversus abdominis plane blocks.[161] However, the protocol had multiple revisions during enrollment and excluded 28% of randomized subjects from the final analysis.[161] Of the 50 excluded participants, total opioid consumption through 72 h was five times *higher* with liposomal bupivacaine added to unencapsulated bupivacaine (52.1 mg) than with bupivacaine hydrochloride alone (10.5 mg).[161]

Explicitly excluded from the Cochrane bias tool is industry funding. It has been demonstrated that "drug and device studies sponsored by manufacturing companies have

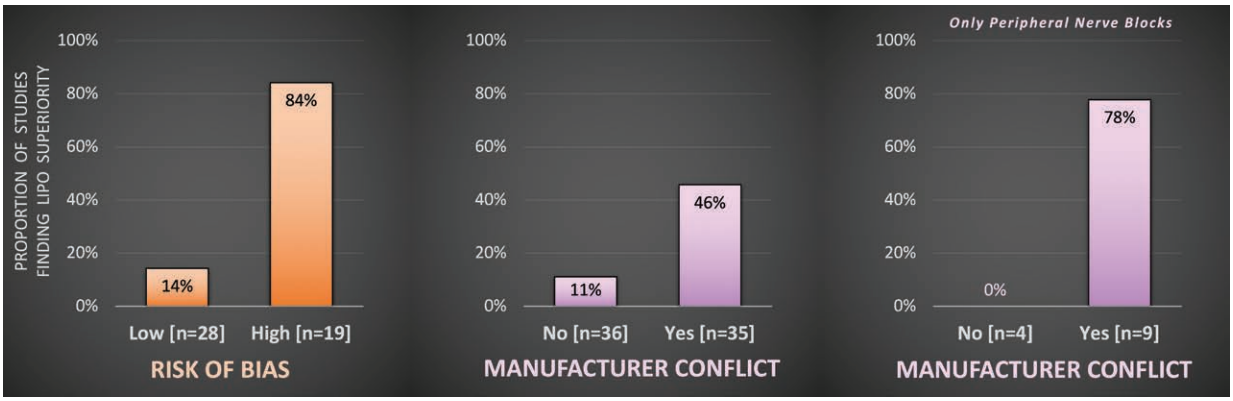

Fig. 2. Correlation between studies with a finding of liposomal bupivacaine superiority over a control and (*A*) overall risk of bias as measured with the Cochrane tool[98,99]; and (*B* and *C*) manufacturer conflict involving study funding, and/or an author as a paid consultant or employee. The right-hand graph (*C*) includes randomized, controlled trials involving exclusively peripheral nerve blocks. The total number of studies included in the category for each column is provided in brackets. Lipo, liposomal bupivacaine.

more favorable efficacy results and conclusions than studies sponsored by other sources."[189] One previously published analysis determined that liposomal bupivacaine was found superior to a control in 67% of studies reporting funding from the manufacturer, while only 7% of studies without such funding detected superiority of liposomal bupivacaine.[6] Within the current review, 35% of studies reported funding from the manufacturer of liposomal bupivacaine (25 of the 71 with conflict of interest statements and excluding one phase I study[167]), and this increased to 49% (35 of 71) for studies with any conflicts including funding or authors who were concurrently paid consultants and/or employees. Liposomal bupivacaine was found superior to a control in 46% (16 of 35) with a conflict present, *versus* only 11% (4 of 36) without (fig. 2). This correlation was strongest among 13 randomized, controlled trials involving exclusively peripheral nerve blocks (excluding a phase I study and two randomized, controlled trials lacking conflict information): liposomal bupivacaine was reported superior to a control in 78% (7 of 9) for studies with a conflict present, *versus* 0% without (0 of 4; fig. 2).

An additional potential source of bias may be found in the choice of comparator/control. For the randomized, active-controlled trials of this review (excluding phase III dose–response studies), the maximum approved dose of liposomal bupivacaine (266 mg) was nearly always used, while the unencapsulated local anesthetic comparator was rarely maximized. This is all the more conspicuous since one of the earliest manufacturer-supported randomized, active-controlled trials used 200 mg of unencapsulated bupivacaine for a comparator—without detecting superiority of liposomal bupivacaine (266 mg).[23] The dose was then lowered for a subsequent study to 150 mg of unencapsulated bupivacaine for the control group—again without detecting superiority of liposomal bupivacaine (266 mg).[31] Ultimately, the most-recent "PILLAR" trial used only 100 mg of unencapsulated bupivacaine for the control group ("finding" a statistical superiority for liposomal bupivacaine, 266 mg,[130,133] yet the difference failing to reach statistical significance if the prospectively-described statistical plan was used).[135,140] Indeed, of the three phase IV manufacturer-supported, multicenter, randomized, active-controlled trials,[114,130,161] the unencapsulated bupivacaine control group included a fraction of the approved maximum[100] or commonly utilized dose for these procedures.[132,168,169]

Conclusions

Whether introduced by surgical infiltration or as part of a peripheral nerve block, the preponderance of current evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics when treating postoperative pain (fig. 3). However, medicine is constantly evolving with ongoing research, and the use of liposomal bupivacaine for postoperative analgesia will certainly be no different. Identified knowledge gaps for future research include the concurrent use of liposomal and unencapsulated bupivacaine in both surgical site infiltration and peripheral nerve blocks[135]; optimizing administration techniques[130,138,190,191]; maximizing comparator local anesthetic dose; comparisons with regional analgesics that are not local anesthetic based[192,193]; prospective registration with a clearly defined primary outcome measure and statistical plan[194]; large cohorts to investigate rare adverse events[195–197]; and additional sustained release local anesthetic formulations.[2,198–203] As noted previously by others,[6] minimizing conflicts of interest should be emphasized. The purported advantages of sustained released over standard local

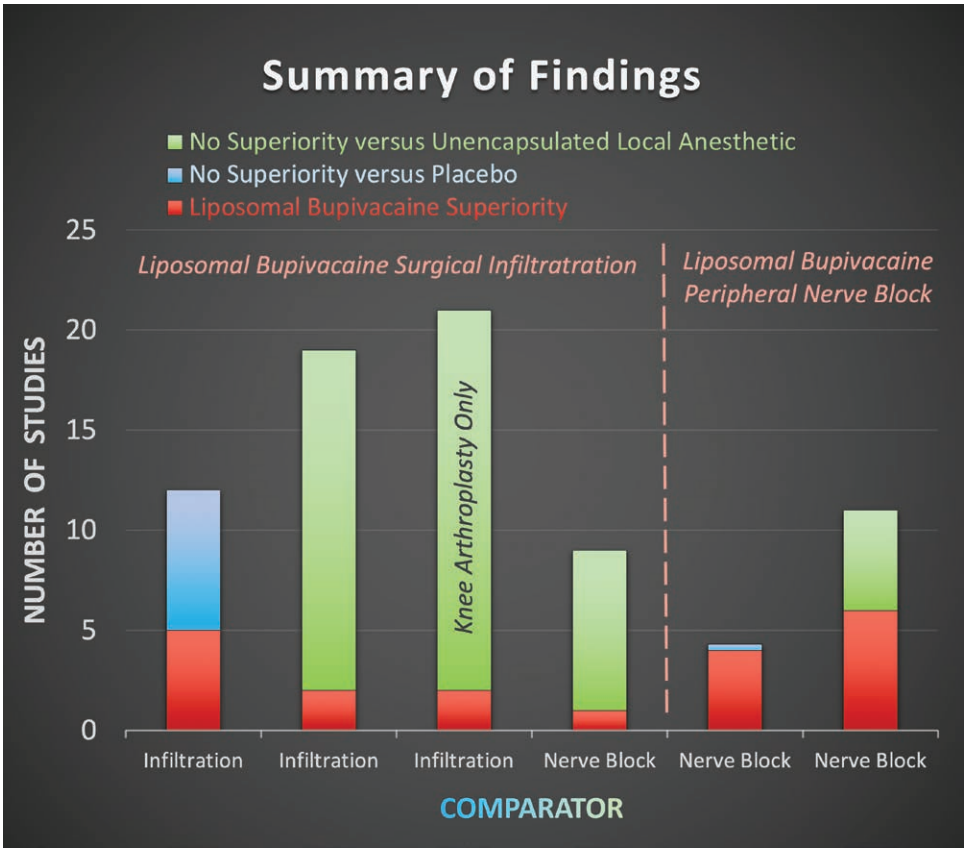

Fig. 3. Summary of findings. A designation of "superior" over the comparator required both statistical significance for the primary outcome measure(s) and clinical significance considered by the study's authors. Note that in the second-to-last column, all four trials report the superiority of liposome bupivacaine over placebo when introduced as part of a peripheral nerve block—the thin blue horizontal line is included only to indicate the comparator was a placebo.

anesthetics in treating acute pain include improved analgesia, decreased opioid requirements, shortened hospitalization, and decreased costs.[22] However, before widespread adoption, it is incumbent on those proposing a switch to liposomal bupivacaine to provide high-quality data from multicenter, randomized, active-controlled trials with a low risk of bias conclusively demonstrating benefits that justify the 100-fold increase in cost over unencapsulated bupivacaine.[123,124,204]

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Competing Interests

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